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Low incidence of focal lesions in the thyroid glands of patients with hereditary haemochromatosis — a single-centre study from Poland

Katarzyna J. Banaszkiewicz [1], ***Katarzyna Sikorska*** [1, 2], ***Damian Panas*** [3], ***Łukasz Obołończyk*** [4], ***Krzysztof Sworczak*** [4]

[1]*Department of Tropical Medicine and Epidemiology, Medical University of Gdańsk, Gdańsk, Poland*
[2]*Department of Tropical and Parasitic Diseases, Chair of Tropical Medicine and Parasitology — National Centre for Tropical Medicine, Institute of Maritime and Tropical Medicine, Gdynia, Medical University of Gdańsk, Gdańsk, Poland*
[3]*Department of Radiological Informatics and Statistics, Medical University of Gdańsk, Gdańsk, Poland*
[4]*Department of Endocrinology and Internal Medicine, Medical University of Gdańsk, Gdańsk, Poland*

Abstract

Introduction: Hereditary haemochromatosis (HH) is a disease characterised by the excessive absorption of iron and its deposition in various organs. Late complications of this disease include cirrhosis, hepatocellular carcinoma, and endocrine disorders. Data from the literature on thyroid disorders in patients with HH are inconsistent and ambiguous, and no research has been done to determine the relationship between excessive accumulation of iron and the thyroid morphology. Therefore, the aim of this study was to characterise thyroid function and ultrasound images in patients with clinically overt hereditary haemochromatosis.

Material and methods: We studied 40 patients who were diagnosed with hereditary haemochromatosis with one of the mutations of the *HFE* gene and iron deposits in liver in specimen from liver biopsies (graded G2 to G4) or in MRI. To assess thyroid function, ultrasound examinations of the thyroid gland were performed and serum TSH concentrations were measured.

Results: We showed in our study that patients with HH have been diagnosed with thyroid focal lesions statistically less frequent than in the control group. We did not reveal any statistically significant difference in TSH concentration between patients with HH and the general population. However, patients with more severe iron deposits in liver showed lower TSH concentration.

Conclusions: Our results indicate lower incidence of focal lesions in thyroid gland in a group of patients with clinically overt hereditary haemochromatosis. **(Endokrynol Pol 2021; 72 (2): 126–132)**

Key words: *haemochromatosis; genetic diseases; iron overload; iron; thyroid; goitre; liver biopsy; MRI*

Introduction

Hereditary haemochromatosis (HH) is a disease characterised by the excessive absorption of iron and its deposition in various tissues of the body. It is one of the most common genetic disorders of metabolism in people [1]. The disease affects 0.24–0.5% of northern European residents. Among white people of western European descent, more than 80% of patients diagnosed with HH are homozygous for a C282Y mutation in the HFE gene. Increased iron absorption was also found in heterozygous carriers of C282Y/H63D and S65C/C282Y mutations [2, 3]. Other alterations in the HFE gene are of uncertain significance, but they may promote the accumulation of iron in the presence of certain factors that affect the physiological regulation of this chemical element [4].

Men are more likely to develop signs and symptoms of HH than women. This is because women naturally lose blood during their menstruation cycles. However, the risk of HH for women increases following menopause. The disease is mainly manifested by fatigue, weakness, decreased libido, joint pain, pain near the right costal margin, dyspepsia, enlarged liver, and moderately elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Late complications in untreated patients include cirrhosis, with a 100-fold higher risk of hepatocellular carcinoma (HCC), diabetes, endocrine disorders (hypogonadism, hypothyroidism, and infertility are among the most frequently quoted ones in literature), heart failure, and severe skin pigmentation disorders [5–8].

Hereditary iron disorders resulting from genetic abnormalities are determined by mutations of *HFE*,

Katarzyna J. Banaszkiewicz, Chair of Tropical Medicine and Parasitology — National Centre for Tropical Medicine, Institute of Maritime and Tropical Medicine, ul. Powstania Styczniowego 9b, 81-519 Gdynia, tel/fax: (+48) 58 622 33 54; e-mail: kbanaszkiewicz@gumed.edu.pl

HJV, *HAMP*, *TfR2*, and *SLC40* genes, which encode, respectively: hephaestin, haemojuvelin, hepcidin, transferrin receptor 2, and ferroportin [9]. One of these proteins, hepcidin, is a hormone that is released in the liver in response to iron overload and inflammation. Decreased levels of hepcidin, observed in patients with hereditary iron overload syndromes, lead to the accumulation of iron in tissues. On the other hand, hepcidin overproduction is common in anaemia of chronic diseases. Another protein, ferroportin, serves as an iron exporter, which is present on the surface of absorptive enterocytes, macrophages, hepatocytes, and trophoblast cells. Interaction of hepcidin with ferroportin resulting in the degradation of hepcidin-ferroportin complex leads to the decrease in the export of cellular iron [10].

In patients suffering from HH and chronic liver disease with advanced fibrosis, the total amount of iron in the organism may exceed 25 g [11]. The iron is mainly deposited in the liver and glandular tissues, i.e. the pancreas, the pituitary gland, the thyroid gland, the gonads, and the adrenal glands. This process may be precisely visualised by using a non-invasive imaging method, i.e. magnetic resonance imaging (MRI) [12, 13]. Two laboratory parameters, ferritin and transferrin saturation, are also used to detect any abnormalities in the accumulation of iron. Not only may they indicate the need to extend the diagnostics for iron overload syndrome, but also, if the syndrome is diagnosed, help to determine the right treatment plan for the patient [14]. The main treatment for haemochromatosis includes bloodletting (therapeutic phlebotomy), a controlled removal of blood from the patient's body, that effectively reduces the amount of iron in the organism. The treatment helps to prevent irreversible organ damage and improves the prognosis and survival rate of patients [15].

Data from literature on thyroid disorders in patients with HH are inconsistent and ambiguous. In a publication from 1983, Edwards et al. showed a higher incidence rate of primary hypothyroidism in patients with HH — the disorder was diagnosed in 8.8% of male patients with HH [16]. However, more recent studies, published by Murphy in 2004, did not confirm that thesis [17]. International guidelines for medical practitioners developed by the European Association for the Study of the Liver (EASL) include recommendations to monitor both thyroid function and testosterone levels (in men) for patients diagnosed with HH [18]. So far, no research has been done to determine the relationship between excessive iron accumulation and greater thyroid volume, which could lead to the formation of goitres or focal lesions in this organ. It is also important to remember about the role of iron in the synthesis of thyroid hormones (TH). The presence of iron seems crucial for the proper functioning of thyroid peroxidase (TPO), because excess iron may stimulate TPO to synthesise TH. On the other hand, iron deposits in the pituitary gland may reduce the concentration of endogenic thyroid-stimulating hormone (TSH).

Thanks to the accessibility of genetic tests, it is currently possible to diagnose increasingly young patients, who have not yet developed signs and symptoms of serious organ pathology, including cirrhosis or heart failure. The assessment of pathological changes within the glandular tissue of these patients also have great significance in terms of their qualification for therapeutic phlebotomy. The aim of this study was to characterise thyroid function and ultrasound images in patients with clinically overt hereditary haemochromatosis.

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Material and methods

The aim of the present single-centre study was to show whether Polish patients diagnosed with, and treated for, primary HH (hereditary haemochromatosis) have a higher risk of thyroid disorders. The eligibility criteria included a C282Y/C282Y, H63D/C282Y, and H63D/H63D mutation in the *HFE* gene (confirmed by a PCR-based test), abnormal iron laboratory parameters in blood (elevated ferritin level of > 200 ng/mL in female patients and > 300 ng/mL in male patients and transferrin saturation > 45%), and excessive iron deposition in the liver (confirmed by either a core needle biopsy of the liver and staining with Prussian blue for presence of iron deposits in hepatocytes assessed at least at grade 2 or by abdominal MRI in which T2-weighted images revealed excessive iron accumulation in the liver*). Participants were informed about the aim of the study, and all of them gave written consent. The study was approved by the Independent Bioethics Committee for Scientific Research at the Medical University of Gdansk (NKBBN/177/2016). The study included 40 participants (12 female patients and 28 male patients) aged from 21 to 73 years (the mean age of patients being 50.35 years), who were diagnosed with hereditary HH. The control group included healthy volunteers, matched for gender and age with the study group, who showed no abnormalities in iron laboratory parameters and no previous history of thyroid disorders. Table 1 presents the eligibility criteria for the study.

The homozygous C282Y/C282Y mutation was confirmed in 29 patients, whereas the H63D/H63D mutation — in 2 patients. Nine patients tested positive for the heterozygous C282Y/H63D mutation (Fig. 1). The excessive accumulation of iron was confirmed in all cases: 26 patients underwent liver biopsy: iron deposits in hepatocytes were assessed as grade 2 or grade 3–4 according to the Scheuer scale (as previously described) [19]. Nineteen specimens had an iron grade of G3/G4, and 7 specimens had an iron grade of G2. The remaining 14 patients underwent MRI of the liver, which confirmed in all cases the presence of iron deposits in this organ, which met the inclusion criteria. All patients were undergoing therapeutic phlebotomy and continued to be followed up in outpatient hepatology clinics. The assessment of patients included iron laboratory parameters in serum, measured at the qualification for the therapeutic phlebotomy and outpatient follow-ups, and the aminotransferase activity in serum, used at the stage of early diagnosis as an indicator of liver damage due to HH.

The distribution of mutations in patients with hereditary haemochromatosis (HH) is shown in Figure 1.

To assess the thyroid morphology and function, the ultrasound examination of the thyroid gland was performed and serum TSH concentrations were measured. The ultrasound examination was performed using a Logiq S7 expert device, and the parenchymal blood flow was visualized by means of colour and power Doppler.

Table 1. *Eligibility criteria for the study included the following: confirmed mutation in the HFE gene and fulfilment of one laboratory criterium and one iron deposition criterium*

Abnormal laboratory results	Confirmed iron deposition	Confirmed mutation in the *HFE* gene
Serum iron concentration > 150 ng/mL	Liver biopsy report, with the inflammatory grade of G2 at least	C282Y/C282Y
or	or	or
Serum ferritin concentration > 200 ng/mL in women or > 300 ng/mL in men	Excessive accumulation of iron on MRI in T2 sequence	H63D/C282Y
or		or
Transferrin saturation > 45%		H63D/H63D

MRI — magnetic resonance imaging

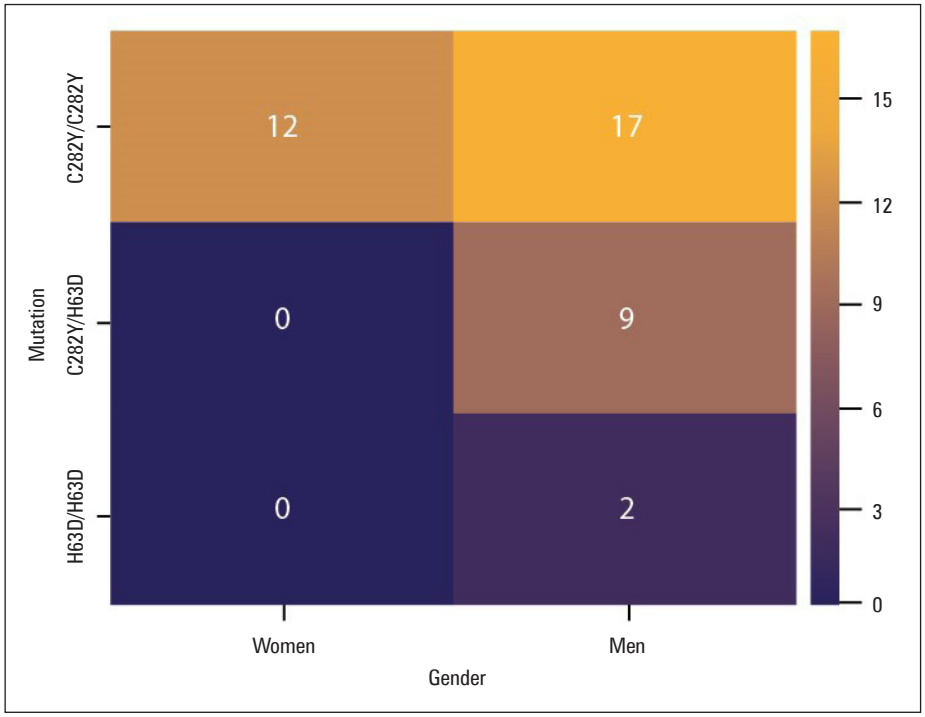

Figure 1. *Distribution of mutations in patients with hereditary haemochromatosis (HH)*

To prevent any errors in measurements, each ultrasound examination was performed by the same medical practitioner, using the same apparatus. The following parameters were evaluated during the examination: thyroid volume in millilitres, echogenicity of the thyroid parenchyma, vascularisation, and the number of focal lesions. The following characteristic features of autoimmune thyroid disease (AITD) were determined: abnormally low echogenicity of the thyroid parenchyma, presence of hyperechogenic bands indicative of fibrosis, areas of lower echogenicity, and abnormal blood flow. To evaluate the thyroid function in all study participants, serum TSH concentrations were measured by means of immunofluorescence. The patients were also asked to fill in a questionnaire, which gathered information about the time from the diagnosis of haemochromatosis and the frequency of bloodlettings. Moreover, the medical history was obtained with the focus on the following disorders of the endocrine system: hypothyroidism and hyperthyroidism, pituitary gland disorders, infertility, hypogonadism, and diabetes.

The characteristics of the study group: patient age, treatment data, and laboratory test results are presented in Table 2. Among 40 patients diagnosed with HH, six (15%) were found to have clinical symptoms of cirrhosis with nodular transformation of the liver and portal hypertension. Histopathological study performed on 26 patients who underwent liver biopsy revealed a fibrosis grade of G0 in eight patients (30.76%), G1 in 13 patients (50%), G2 in three patients (11.53%), and G3/G4 in two patients (7.69%). Twenty-three patients had endocrine disorders that had been diagnosed before the study enrolment, which are summarised in Table 3.

The control group included 20 patients (10 women and 10 men) with no previous history of thyroid disorder or family history of thyroid cancer. The mean age was 48.10 years (SD = 14.73). There was no statistically significant difference between the study group and the control group in this respect ($p = 0.05$, test U).

The results were statistically analysed using Python (version 3.7.4). Statistical tests were performed using SciPy (version 1.2.1), and the diagrams were created by means of Seaborn (version 0.9.0). Because the assumption of normal data distribution was not fulfilled, the groups were compared using nonparametric Mann-Whitney U test and, in the case of qualitative data, the Fisher's exact test. For the correlation between quantitative features, the Pearson's linear correlation coefficient was determined. The significance level was set at 0.05.

Table 2. *Study group — overview*

	Mean (SD)	Me	Min–max
Age at study enrolment [years]	50.35 (14.59)	51.5	21–73
Age at diagnosis	43.27 (12.75)	42.5	21–70
Number of phlebotomies	25.53 (42.49)	14.5	1–205
Maximum ferritin concentration [ng/mL]	918.40 (799.03)	689.0	126–3550
Mean ferritin concentration [ng/mL]	554.37 (509.06)	347.5	60–2183
ALT (0–41 U/l)	44.62 (27.27)	38.0	12–117
AST (0–40 U/l)	32.25 (15.28)	30.0	8–77
Transferrin saturation (20–40%)	79.25 (17.47)	86.5	30–100

ALT — alanine aminotransferase; AST — asparagine aminotransferase; SD — standard deviation; Me — median; min — minimum value; max — maximum value

Table 3. *Endocrine disorders diagnosed in the study group*

Number of patients (%)	
Hypothyroidism	4 (10)
Hyperthyroidism	1 (2.5)
Diabetes or pre-diabetes stage	14 (35)
Positive antithyroid antibody test results	3 (7.5)
Goitre	2 (5)
Status post strumectomy due to a goitre	1 (2.5)

Table 4. *Group comparison*

	Control (n = 20)	Study (n = 40)
TSH (0.35–4.94 uU/mL)	p = 0.239[a]	
Mean (SD)	1.10 (0.54)	1.37 (0.87)
Me	0.94	1.13
Min–max	0.48–2.33	0.44–4.58
Thyroid volume [mL]	p = 0.358[a]	
mean (SD)	12.81 (5.10)	16.37 (11.92)
Me	11.25	13.85
min–max	7.70–25.00	5.00–48.00
AITD	p = 0.304[b]	
n (%)	2 (10)	10 (25)
Thyroid focal lesions	p = 0.024[b]	
n (%)	9 (45)	9 (22.5)

AITD — autoimmune thyroid disease; TSH — thyroid-stimulating hormone; n — number; SD — standard deviation; Me — median; min — minimum value; max — maximum value; [a]Mann-Whitney U test; [b]Fisher's exact test

Results

Ultrasound examination of the thyroid gland in patients with haemochromatosis revealed the following: signs of AITD in nine patients (22.5%), thyroid focal lesions in seven patients (17.5%), and simple goitres in two patients (5%). One patient after strumectomy presented signs of AITD in the remaining thyroid parenchyma. In 22 patients (55%) the ultrasound findings were normal. In comparison, in the control group of 20 patients, ultrasound findings were normal in nine patients (45%), focal lesions were found in nine patients (45%), and signs of AITD were identified in two patients (10%). Thyroid volumes in the examined and control group did not differ significantly. Three patients with HH (7.5%) had elevated levels of antithyroid antibodies, as found in their medical records. None of the patients, however, required substitution with L-thyroxine (Tab. 4, 5).

In tests evaluating the thyroid function, the mean TSH concentration was 1.39 IU/mL (SD = 0.87) for the study group. Hypothyroidism requiring L-thyroxin supplementation was found in five patients (four patients [10%] due to AITD, one patient [2.5%] after strumectomy). In one patient, laboratory findings revealed hyperthyroidism due to a nodular goitre. One patient had a diagnosis of Graves' disease (currently in remission).

In the control group, the mean thyroid volume was 16.35 mL (SD = 8.90), and the mean TSH concentration was 1.10 IU/mL (SD = 0.54). No statistically significant differences comparing to HH patients were found for these two parameters. The ultrasound examination revealed nodular goitres in nine patients (45%) and signs of AITD in two patients (10%). In the remaining nine patients (45%), the ultrasound findings were normal. More specific gender-disaggregated data can be found in Table 5.

In the group of patients with severe deposition of iron in the liver, significant differences in TSH concentrations were found. In the group with iron grade of G3 or G4, there was a statistically lower TSH concentration (Fig. 2).

Discussion

The study attempted to analyse the thyroid dysfunctions in patients diagnosed with hereditary haemochromatosis. Due to the capacity of iron to deposit

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Table 5. *Comparison of the study group and the control group, based on selected parameters*

	Women		Men	
	Control (n = 10)	**Study (n = 12)**	**Control (n = 10)**	**Study (n = 28)**
TSH (0.35–4.94 uU/mL)	p = 0.346[a]		p = 0.264[a]	
Mean (SD)	0.94 (0.35)	1.01 (0.37)	1.27 (0.66)	1.52 (0.98)
Me	0.78	0.95	0.97	1.29
Min–max	0.48–1.56	0.44–1.80	0.50–2.33	0.45–4.58
Thyroid volume [mL]	p = 0.358[a]		p = 0.434[a]	
Mean (SD)	12.81 (5.10)	16.37 (11.92)	19.90 (10.65)	17.68 (5.34)
Me	11.25	13.85	18.65	18.00
Min–max	7.70–25.00	5.00–48.00	10.00–46.00	7.00–27.00
AITD	p = 0.015[b]	p = 0.304[b c]	p = 0.622[b]	
n (%)	0 (0.00)	6 (50.00)	2 (20.00)	4 (14.30)
Focal lesions	p = 0.192[b]	p = 0.024[b c]	p = 0.152[b]	
n (%)	6 (60.00)	3 (25.00)	3 (10.00)	3 (10.00)

TSH — thyroid-stimulating hormone; n — number; SD — standard deviation; Me — median; min — minimum value; max — maximum value; [a]Mann-Whitney U test; [b]Fisher's exact test; [c]comparison without gender disaggregation

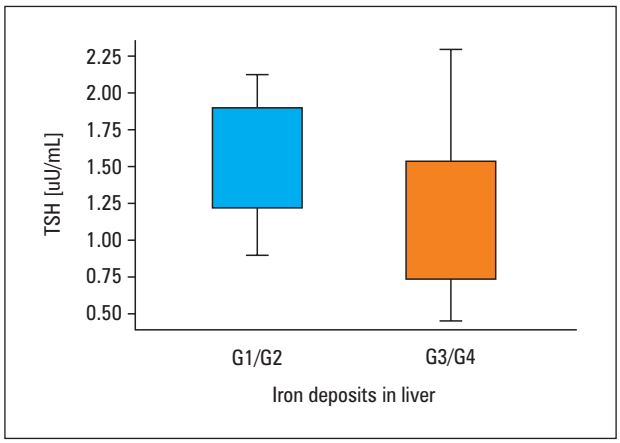

Figure 2. *In the group with severe iron deposition confirmed by liver biopsy (the iron deposits of G3 or G4), there was a statistically significant lower TSH concentration (p value = 0.005, test u)*

in the glandular tissue, including the thyroid gland, a hypothesis was formed that iron overload may be significant for the pathophysiology of thyroid disorders.

Thyroid diseases are a serious problem in Poland. According to the data of the Main Statistical Office, in 2006, 22% of the Polish population suffered from thyroid diseases, including 2% from hypothyroidism [20]. Based on thyroid ultrasound screening tests, the frequency of focal lesions in the thyroid gland is estimated at 19–67% [21]. The latest screening study in the Polish population — the Thyroid Disease Prevention Program implemented in the years 2006–2011 — allowed the diagnosis of thyroid focal lesions in 44.1%, and the frequency is very similar in our small control group [22].

In the study of the group of patients with HH, focal lesions were significantly less common than in the control group (22.5% vs. 45%) and in the general population [22], which is associated with a lower risk of neoplastic lesions. A study from 2018 found that iron deficiency impairs the synthesis of thyroxine (T4) and its conversion to triiodothyronine (T3) [23]. A cross-sectional study of schoolchildren in Iran published in 2002 showed that iron deficiency is associated with a high prevalence of goitre [24]. Our study put forward the hypothesis that in conditions of extremely high iron content in body, the opposite phenomenon may occur. This was reflected in the present study, in which the rate of thyroid focal lesions in patients with HH was significantly lower than in the control group.

It is also worth emphasising the role of iron in the production of peripheral thyroid hormones: iron is a microelement that has a potential influence on thyroid hormone deficiency. In the first two steps of thyroid hormone synthesis, thyroperoxidase, which is iron-dependent, acts as a catalyst [25]. Studies on human beings and animals showed that iron deficiency in the blood translates into a lower concentration of thyroid hormones, hinders the conversion of T4 to T3, and stimulates the pituitary gland to release thyrotropin. Adult patients with iron deficiency have lower concentrations of T4 and T3 and higher TSH levels when compared to the control group [26]. In the population at risk of iodine deficiency, iodine supplementation is much more effective with sufficient iron intake, which also has a protective effect against the formation of thyroid goitres in the group of patients who receive such supplementation [27].

A new study published by Polish authors in 2019 in Scientific Reports showed significant differences in hepcidin levels in patients with newly diagnosed Hashimoto's disease and after hormonal treatment. Along with administration of L-thyroxine, there was a significant decrease in serum hepcidin concentration, which proves that the activity of this protein, which is significantly involved in the pathophysiology of HH, changes in the case of thyroid dysfunction [28].

The present study did not reveal any statistically significant differences in TSH concentrations between patients with HH and the general population. The findings are consistent with the results of the HEIRS study, which showed that patients with a homozygous C282Y mutation are not at a higher risk of thyroid diseases than the general population. It should be noted, however, that the HEIRS study focused only on the genotype characteristic of HH and did not investigate the concentration of iron in internal organs. Patients with the C282Y mutation constitute from 10% to 30% of HH cases, and therefore participants of the present study had to fulfil laboratory, histopathological, or imaging criteria in addition to developing a haemochromatosis phenotype. This made it possible to analyse not only the mutation in the HFE gene, but also the influence of iron concentration on the thyroid morphology. Taking into account the deposition of iron in internal organs, it was shown that patients with a higher level of iron in the organism (numerous iron deposits confirmed by a biopsy and high transferrin saturation) have lower TSH concentrations. This could be related either to a more effective production of peripheral hormones, which lowers the TSH level, or to iron deposits in the pituitary gland, which lead to the destruction of thyrotropin cells and impair their releasing ability. A lower TSH concentration was also noted in patients with more severe iron deposition. The mechanism responsible for this phenomenon is unclear and requires further analysis.The role of iron in carcinogenesis, especially hepatocellular, is well known, but when it comes to the thyroid gland this issue can look very different. In the latest publication from 2020, it was demonstrated that silencing of transferrin-1 receptor (TfR-1) plays a role in inhibiting carcinogenesis pathways for follicular and anaplastic thyroid cancer. Under the conditions of high serum iron concentration, TfR-1 downregulation occurs due to IRP-IRE-related mechanisms (iron regulatory protein — iron responsive element), and carcinogenesis pathways are inhibited [29].

Autoimmune thyroid disease affects all age groups, and the incidence rate varies from 0.3 to 1.5%, which is probably underestimated – in pathology studies the disease is diagnosed in 14–17% of patients. The key role in diagnosing the disease is played by the following: 1 — TSH test, 2 — measurement of antithyroid antibodies (antithyroglobulin antibodies (aTg), anti-thyroid peroxidase antibodies (aTPO), and thyroid-stimulating hormone receptor antibodies (TRAb), and 3 — thyroid ultrasound. In the group of patients with HH, signs of AITD were more commonly detected during an ultrasound examination than in the control group (they occurred in 22.5% of all patients). However, given the small population sample, no statistical significance was found.

In a study from 1984 [16], 49 C282Y-homozygous patients were evaluated for thyroid disorders — the thyroxine and thyrotropin serum concentrations were also measured. It was shown that 3 out of 34 male participants (8.7%) had hypothyroidism. The patients were found to have elevated levels of antithyroid antibodies in blood tests and lymphocytic infiltrations in histopathological samples of the thyroid gland. The authors justified the greater rate of AITDs with the stimulating influence of iron on the autoimmune response in the glandular tissue. What is interesting, none of the 15 female patients in the study was diagnosed with any thyroid disorder. According to the authors, this may be related to a more intense iron overload in men diagnosed with HH than in women. However, due to the small population sample, no statistical significance was shown. In our HH group also we did not diagnose women with AITD. It would be necessary to conduct a further study, in which a larger sample of patients with HH would undergo thyroid function assessment and immune status evaluation.

A study by Murphy et al., published in 2004, questioned the correlation between thyroid disorders and HH. In the study, which involved a group of 154 patients with HH, haemochromatosis was confirmed by genetic tests, increased ferritin concentrations in the blood, and the presence of iron in liver samples. In the study, the patients were also treated with therapeutic phlebotomy. As part of the study, serum TSH concentrations as well as fT4 concentrations and the level of antithyroid antibodies were all assessed. Five patients were found to have an impaired thyroid function, and only one patient developed fully-blown AITD that required L-thyroxine supplementation. In two cases, the level of antithyroid antibodies was elevated. Based on the findings, the authors suggested that thyroid disorders are not so common in patients with HH. Thus, our study seems to shed more light on the links between iron overload and thyroid disorders by the use of ultrasound imaging of this gland.

Conclusions

The present study did not show any significant differences in the thyroid volume and TSH concentrations between patients with hereditary haemochromatosis

and the general population. However, patients with HH were less frequently diagnosed with thyroid focal lesions in USG. Nevertheless, the mechanisms behind this phenomenon remain unclear.

The role of iron in the pathogenesis of AITD and its connection with gender is yet to be examined. An abnormal ultrasound image of the thyroid gland, which could be responsible for AITD, was more common in the study group, but no significant difference was revealed. Therefore, it is not known whether this abnormality was caused by iron deposits in the organ. It would be necessary to conduct a further study, in which a larger sample of patients with HH would undergo thyroid function assessment, immune status evaluation, and imaging tests by means of ultrasound and MRI of the thyroid gland — an alternative method for diagnosing iron deposition in the thyroid gland.

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