

# Thyroid diseases in the course of Crohn's disease

## Choroby tarczycy w przebiegu choroby Leśniowskiego-Crohna

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**Key words:** Hashimoto's disease, Graves-Basedow disease, Crohn's disease, autoimmunisation.

**Słowa kluczowe:** choroba Hashimoto, choroba Gravesa-Basedova, choroba Leśniowskiego-Crohna, autoimmunizacja.

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### Abstract

**Introduction:** In recent years, more and more attention has been given to the possibility of the co-occurrence of diseases grounded in autoimmune disorders. Recognizing the coexistence of two or a larger number of diseases, in the pathogenesis of which autoimmune disorders play a role, allows modification of treatment in order to achieve early improvement of the patient's general condition. It is generally known that autoimmune disorders play a role in the pathogenesis of Crohn's disease. What is more, it is also known that Hashimoto type thyroid gland inflammation and Graves-Basedow disease are the most frequent diseases with an autoimmune basis.

**Aim:** To analyse the condition of patients with Crohn's disease from the point of view of chronic Hashimoto type thyroid gland inflammation co-occurrence.

**Material and methods:** In the research we examined a group of 58 patients (31 women and 27 men) with diagnosed Crohn's disease in endoscopic and histopathological examination and a research sample (23 women and 22 men) with an affected abdominal cavity without any nonspecific inflammation diagnosed. All of the patients were over 16 years old and gave their consent for participation in the examination. The following examinations were made in the analysed groups: TSH, aTPO, aTG, TSHR.

**Results:** As a result of the analysis, a statistically significant increase of the frequency of thyroid gland function disorders in patients with Crohn's disease was found.

**Conclusions:** Therefore, it seems to be advisable to consider the implementation of diagnostics for thyroid gland diseases in patients with diagnosed Crohn's disease and the treatment of a possible coexisting disease of the thyroid gland may accelerate the acquisition and maintenance of long-term remission of the essential disease.

### Streszczenie

**Wstęp:** W ostatnich latach coraz większą uwagę zwraca się na współwystępowanie schorzeń, u podłoża których leżą zaburzenia autoimmunologiczne. Rozpoznanie współistnienia dwóch lub większej liczby chorób, w których patogenezie odgrywają rolę zaburzenia autoimmunologiczne, pozwala na modyfikację leczenia w taki sposób, aby uzyskać wcześniejszą poprawę stanu ogólnego chorego. Wiadomo, że w patogenezie choroby Leśniowskiego-Crohna istotną rolę odgrywają zaburzenia autoimmunologiczne, a do najczęstszych schorzeń o podłożu autoimmunologicznym zalicza się przewlekłe zapalenie tarczycy typu Hashimoto i chorobę Gravesa-Basedova.

**Cel:** Analiza stanu zdrowia osób z chorobą Leśniowskiego-Crohna pod kątem współwystępowania z przewlekłym zapaleniem tarczycy typu Hashimoto lub chorobą Gravesa-Basedova.

**Materiał i metody:** Do badania włączono grupę 53 osób, w tym 31 kobiet i 27 mężczyzn, z rozpoznaną w badaniach endoskopowych i histopatologicznych chorobą Leśniowskiego-Crohna, oraz grupę kontrolną obejmującą 45 pacjentów, 23 kobiety i 22 mężczyzn, z dolegliwościami ze strony jamy brzusznej, u których nie stwierdzono nieswoistego zapalenia. Wszyscy pacjenci ukończyli 16 lat i wyrazili zgodę na udział w badaniu. W analizowanej grupie wykonano badania, m.in.: TSH, aTPO, aTG, aTSHR.

**Wyniki:** W wyniku przeprowadzonej analizy wykazano statystycznie istotne zwiększenie częstości występowania zaburzeń funkcji tarczycy u osób z chorobą Leśniowskiego-Crohna.

**Wnioski:** Wydaje się, że wdrożenie diagnostyki w kierunku chorób tarczycy u osób z rozpoznaną chorobą Leśniowskiego-Crohna jest celowe, a leczenie ewentualnej współistniejącej choroby tarczycy może przyspieszać uzyskanie i utrzymanie przez dłuższy czas remisji choroby podstawowej.

## Introduction

In recent years there has been more and more communication about co-occurrence of diseases caused by autoimmune disorders [1-3].

Autoimmune reactions are related to processes happening inside of the system, aimed against an own antigen or a group of own antigens [4]. Autoimmune disorders are related to the lack of distinction of the immune system between own and strange antigens. In consequence of these processes own tissues are destroyed.

In the literature we find that the most common autoimmune disorder is Hashimoto's thyroiditis. The morbidity rate of this disease is 0.3-1.5 cases for 1000 patients per year [5]. The most frequent cause of hyperthyroidism is Graves-Basedow disease [6, 7]. Recently an increase of the morbidity rate of nonspecific enteritis, e.g. Crohn's disease, has been observed [8, 9]. In the pathogenesis of Crohn's disease the autoimmune reactions are vital [10, 11]. As we know, the autoimmune reaction for one epitope (a fragment of antigen) can be extended to more epitopes of the same or different antigens, which in consequence can result in disorders of many organs. We also know that the occurrence of antibodies in blood, tested by laboratory methods, can be an important diagnostic marker and a predictor of many diseases from this group.

The high number of instances of co-occurrence of diseases caused by autoimmune disorders [9, 12-15] convinced us to investigate patients suffering from Crohn's disease in terms of co-occurrence with the most common autoimmune disorder diseases, that is Hashimoto's thyroiditis and Graves-Basedow disease.

Crohn's disease is a persistent, transmural, usually granulomatous inflammation of the gastrointestinal tract, which can pertain to all its segments from the oral cavity up to the anus. Areas affected by the inflammation can be separated by segments of alimentary tract without inflammation. The inflammation progresses in bowel mucosa, gradually extending to all the layers of its wall, with subsequent fibrosis. The results of this process can be fistula and constriction with all the consequences. The most common symptoms of this disease are stomach aches, diarrhoea rarely with blood, asthenia, fever and bad absorption. Although in many cases periods of exacerbation and remission are observed, usually symptoms are chronic and cause disability. In a 10-year period of the disease about 10% of patients have an operation because of disease complications (fistula, abscess, gastrointestinal tract obstruction, rectal distention, perforation, bleeding, and bowel cancer). In pathogenesis of Crohn's disease genetic, environmental and immune factors are important. This disease occurs 0.5 times less often than ulcerative coli-

tis, which is the most common form of bowel inflammation and slightly more frequent in women, the average age of sufferers being 15-25 [8-11].

Graves-Basedow disease is an autoimmune thyroid disease in the course of which antibodies against thyroid-stimulating hormone receptors (aTSHR) are created. The receptor is a cell membrane protein of thyroid cells. The consequence of it is stimulation of thyroid cells and hyperthyroidism with all the symptoms (crop, rapid arrhythmia, auricular fibrillation, myokymia, higher motor activity, eyelid retraction, weight loss etc.). Due to the fact that the same antigen is present in both thyroid cell and eye socket fibroblasts, Graves' orbitopathy occurs quite often. The aetiology of Graves-Basedow disease is similar to nonspecific bowel inflammation [5].

Hashimoto's thyroiditis is a persistent, autoimmune inflammation of the thyroid, also called lymphocytic inflammation, in the course of which antibodies against thyroperoxidase (aTPO) and thyroglobulin (aTG) are produced. It is the most common type of thyroid inflammation, the most common cause of its hypofunction and the most common autoimmune disease. In the course of thyroid inflammation lymphocytic infiltrations occur. It may be accompanied by euthyroidism or thyroid hypofunction. Apart from aTPO and aTG antibodies in some cases antibodies blocking the TSH receptor are discovered. Inflammation, progressive and persistent, can occur together with crop, proper size of thyroid or atrophica. Symptoms cause slowing down of metabolism (weight gain, weakness, tiredness, attention deficit, problems with memory, feeling cold and obstruction) [5-7].

## Aim

The aim of the work was to evaluate thyroid gland function in patients with Crohn's disease diagnosed on the endoscopic and histopathological basis.

## Material and methods

The examination included 58 patients with documented Crohn's disease and 45 patients with abdominal cavity disorders. All the patients were over 16 years old and gave their consent for participation in the examination. The following examinations were performed: morphology, TSH, aTG, aTPO, aTSHR. In the case of abnormal results of the examinations a procedure according to endocrinological standards was implemented.

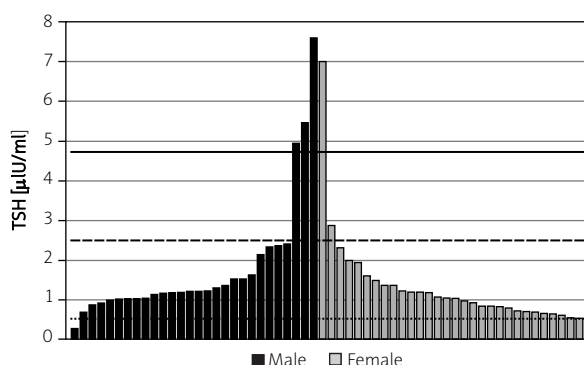
Research findings were analysed in groups according to the sex:

- men with diagnosed Crohn's disease – 27 (44.55%),
- women with diagnosed Crohn's disease – 31 (53.45%),
- men in the research sample – 22 (48.89%),
- women in the research sample – 23 (51.11%).

**Table I.** Percentage rate of raised TSH level with division into sexes in patients with diagnosed Crohn's disease  
**Tabela I.** Rozkład procentowy zwiększonych stężeń TSH u pacjentów z chorobą Leśniowskiego-Crohna z podziałem na płeć

	Male		Female	
	TSH > 4.78 $\mu$ IU/ml	TSH > 2.5 $\mu$ IU/ml	TSH > 4.78 $\mu$ IU/ml	TSH > 2.5 $\mu$ IU/ml
Patients with CD	2 (7.41%)	2 (7.41%)	2 (6.45%)	3 (9.68%)

The values of TSH levels, glycoprotein stimulating hormonogenesis of the thyroid gland were analysed for screening assessment of the gland function, separately in the group of women and men. The assessment of antithyroid antibody levels was performed, i.e. antithyroglobulin antibodies (aTG), antibodies against thyroid glycoprotein which is the main component of the thyroid colloid, which determines the matrix for the synthesis of thyroid hormones and the assessment of the level of thyroid peroxidase antibodies (aTPO), i.e. antibodies directed against thyroid peroxidase – a glycoprotein enzyme taking part in the synthesis of thyroid hormones and the assessment of antireceptor thyroid antibody level (aTSHR).



**Fig. 1.** Quantitative rate of the of TSH level with division into sexes in patients with diagnosed Crohn's disease

**Ryc. 1.** Rozkład ilościowy poziomu TSH z podziałem na płeć u pacjentów z rozpoznaną chorobą Leśniowskiego-Crohna

**Table II.** Percentage rate of lowered TSH level with division into sexes in patients with diagnosed Crohn's disease

**Tabela II.** Rozkład procentowy zmniejszonych stężeń TSH z podziałem na płeć u pacjentów z chorobą Leśniowskiego-Crohna

	Male (TSH < 0.55 $\mu$ IU/ml)	Female (TSH < 0.55 $\mu$ IU/ml)
Patients with CD	1 (3.70%)	1 (3.23%)

### Statistical analysis

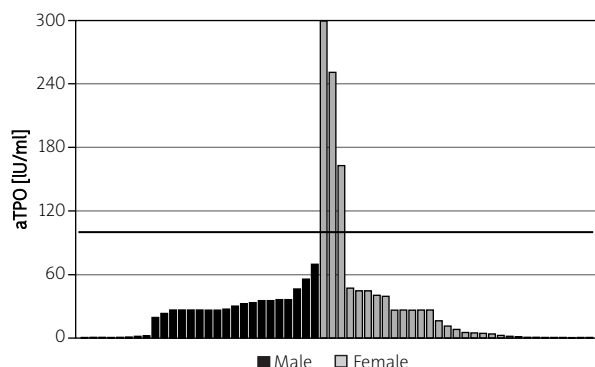
The main statistical tool was the analysis of frequency level in each group. Statistical significance was established as 5% ( $p = 0.05$ ).

### Results

The TSH test results in the examined group with the division into sex is presented in Figure 1. Upper limit of the norm (TSH = 4.78  $\mu$ IU/ml) was marked on the graph with a thick continuous line. Lower limit of the norm (TSH = 0.55  $\mu$ IU/ml) was marked with a dotted line. At the present time the endocrinologists' circles submit a high TSH level, accepted as the norm, for consideration. They suggest lowering this level to the value of 2.5  $\mu$ IU/ml (marked on the graph with a broken line). Lowering the upper limit of TSH is consequent to the fact that 95% of the population fits the norm between 0.4 and 2.5  $\mu$ IU/ml [17, 18]. In the group of men with diagnosed Crohn's disease a raised TSH level TSH > 4.78  $\mu$ IU/ml was found in about 7.41% and in the same number the TSH level was > 2.5  $\mu$ IU/ml. Analogically, in the group of women TSH > 4.78  $\mu$ IU/ml was found in about 6.45% and TSH > 2.5  $\mu$ IU/ml in 9.68% of patients. Overall data are presented in Table I. Establishing the statistical significance threshold as 5% ( $p = 0.05$ ) in the research sample we can observe a statistically significant increase of TSH value in all the groups independently of sex. Analogically, the analysis of lowered TSH level in particular groups is shown in Table II. Analysing the above scheme, one should note that the correlation of the lowered TSH level in patients with Crohn's disease (in both sexes) is below the level of statistical significance.

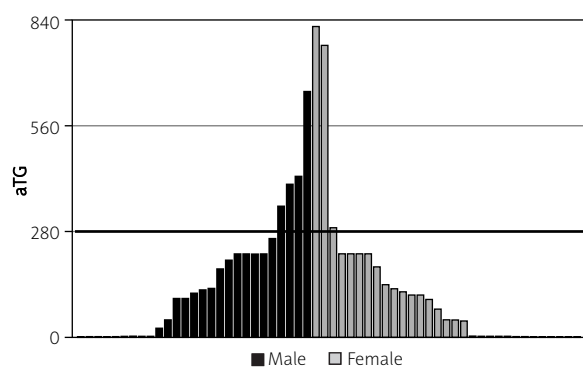
The aTPO test results are presented in the Figure 2. The upper limit of the norm (aTPO = 100 IU/ml) was marked with a thick line on the graph. Table III presents the overall data. A statistically significant increase of antiperoxidase antibody levels is seen only in the analysed group of women. Additionally, in the analysed group, no case of positive levels of aTPO antibodies in men with diagnosed Crohn's disease was documented.

Results of the aTG level in the examined sample with the division into sexes are shown in Figure 3. The upper limit of the norm (aTG = 280 IU/ml) was marked with a thick line. The overall data are presented in Table IV. Analysis of the level of antithyroglobulin antibodies



**Fig. 2.** Quantitative rate of the aTPO level with division into sexes in patients with diagnosed Crohn's disease

**Ryc. 2.** Rozkład ilościowy stężeń aTPO z podziałem na płeć u pacjentów z rozpoznaną chorobą Leśniowskiego-Crohna



**Fig. 3.** Quantitative rate of the aTG level with division into sexes in patients with diagnosed Crohn's disease  
**Ryc. 3.** Rozkład ilościowy stężeń aTG z podziałem na płeć u pacjentów z rozpoznaną chorobą Leśniowskiego-Crohna

**Table III.** Percentage rate of raised aTPO level with division into sexes in patients with diagnosed Crohn's disease  
**Tabela III.** Rozkład procentowy zwiększonych stężeń aTPO z podziałem na płeć u pacjentów z rozpoznaną chorobą Leśniowskiego-Crohna

	Male		Female	
	aTPO > 60 IU/ml Doubtful and positive	aTPO > 100 IU/ml Positive	aTPO > 60 IU/ml Doubtful and positive	aTPO > 100 IU/ml Positive
Patients with CD	1 (3.70%)	0 (0.00%)	3 (9.68%)	3 (9.68%)

**Table IV.** Percentage rate of raised aTG level with division into sexes in patients with diagnosed Crohn's disease

**Tabela IV.** Rozkład procentowy zwiększonych stężeń aTG z podziałem na płeć u pacjentów z rozpoznaną chorobą Leśniowskiego-Crohna

	Male (aTG > 280 IU/ml)	Female (aTG > 280 IU/ml)
Patients with CD	4 (14.81%)	3 (9.68%)

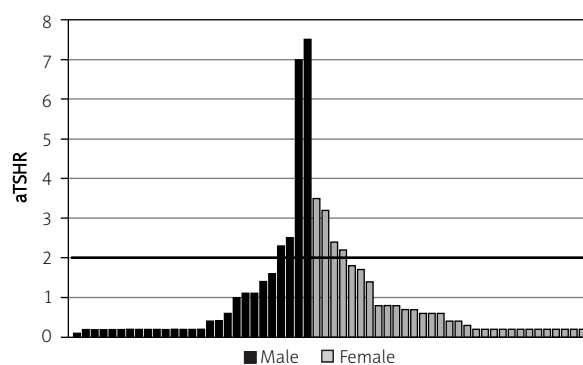
**Table V.** Percentage rate of raised aTSHR level with division into sexes in patients with diagnosed Crohn's disease

**Tabela V.** Rozkład procentowy zwiększonych stężeń aTSHR z podziałem na płeć u pacjentów z rozpoznaną chorobą Leśniowskiego-Crohna

	Male (TSHR > 2 IU/ml)	Female (TSHR > 2 IU/ml)
Patients with CD	4 (14.81%)	4 (12.90%)

suggests a statistically significant increase of its level in the examined sample (both in men and in women).

Results of aTSHR level in the examined sample with division into sexes are shown in Figure 4. The upper norm



**Fig. 4.** Quantitative rate of aTSHR level with division into sexes in patients with diagnosed Crohn's disease

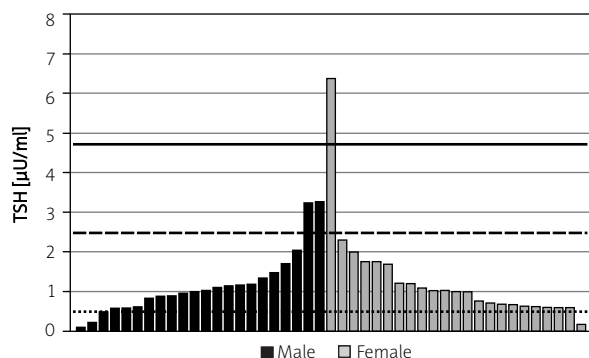
**Ryc. 4.** Rozkład ilościowy stężeń aTSHR z podziałem na płeć u pacjentów z rozpoznaną chorobą Leśniowskiego-Crohna

limit (aTSHR = 2 IU/ml) was marked with a thick line. The overall data of raised aTSHR level are presented in Table V. The analysis of antireceptor antibody levels suggests a significant statistical increase in their level in the whole research sample (both in men and women).

Results of the TSH test in the examined research sample with division into sexes are shown in Figure 5.

**Table VI.** Percentage rate of raised TSH level with division into sexes among the research sample  
**Tabela VI.** Rozkład procentowy zwiększonych stężeń aTPO z podziałem na płeć u pacjentów z grupy kontrolnej

	Male		Female	
	TSH > 4.78 $\mu$ IU/ml	TSH > 2.5 $\mu$ IU/ml	TSH > 4.78 $\mu$ IU/ml	TSH > 2.5 $\mu$ IU/ml
Research sample	0 (0%)	2 (5.13%)	1 (1.59%)	1 (1.59%)

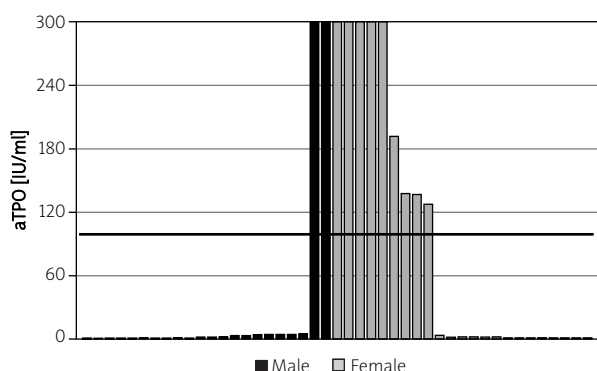


**Fig. 5.** Quantitative rate of the TSH level with division into sexes of patients in the research sample  
**Ryc. 5.** Rozkład ilościowy stężeń TSH z podziałem na płeć u pacjentów z grupy kontrolnej

**Table VII.** Percentage rate of lowered TSH level with division into sexes among the research sample

**Tabela VII.** Rozkład procentowy zmniejszonych stężeń TSH z podziałem na płeć u pacjentów z grupy kontrolnej

	Male	Female
	(TSH < 0.55 $\mu$ IU/ml)	(TSH < 0.55 $\mu$ IU/ml)
Research sample	3 (7.69%)	1 (1.59%)



**Fig. 6.** Quantitative rate of aTPO with division into sexes among the research sample  
**Ryc. 6.** Rozkład ilościowy stężeń aTPO z podziałem na płeć u pacjentów z grupy kontrolnej

The upper norm limit (TSH = 4.78  $\mu$ IU/ml) was marked on the graph with a thick continuous line. A dashed line was used to mark the upper norm limit providing its reduced value (TSH = 2.5  $\mu$ IU/ml). A dotted line marks the lower norm limit (TSH = 0.55  $\mu$ IU/ml). In the research group of men a raised level of TSH > 4.78  $\mu$ IU/ml was not found, although providing that the upper norm limit is TSH = 2.5  $\mu$ IU/ml raised levels of TSH were observed in 5.13% of those examined. Analogically, in the group of women TSH > 2.5  $\mu$ IU/ml and TSH > 2.5  $\mu$ IU/ml was observed in 1.59% of those examined. The overall data are presented in Table VI.

The analysis of TSH level indicates that in all the research samples, independently of sex, no statistically higher frequency of raised TSH levels occurred (in the groups of men with the assumption that the upper TSH limit is > 2.5  $\mu$ IU/ml the frequency of higher TSH level occurrence was at the border of statistical significance).

Analogically, the analysis of lowered TSH level in particular groups is shown in Table VII. Analysing the above, one should note that in the research sample, statistically significant frequency of lowered TSH level occurs only in the groups of men. In the group of examined women the frequency is not statistically significant.

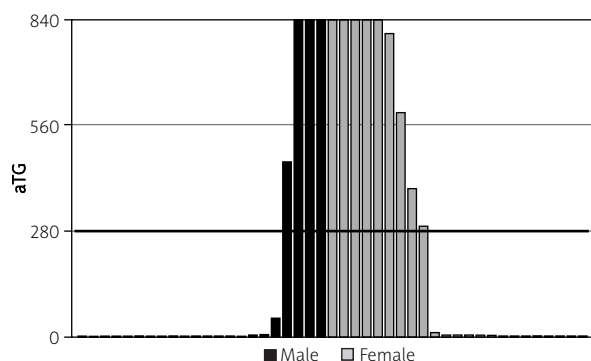
Results of the aTPO test with division into sexes are presented in the following figure (Figure 6). The upper norm limit (aTPO = 100 IU/ml) was marked with a thick line. Results of the aTPO test are presented in the following figure. The overall data are shown in Table VIII. A statistically significant increase of antiperoxidase antibodies can be noted in all the analysed research samples, although in the group of men this quantity is at the border of statistical significance.

Results of the aTG level in the research sample with division into sexes are presented in Figure 7. The upper norm limit (aTG = 280 IU/ml) was marked with a thick line. The overall data of the increased aTG level are presented in Table IX. The analysis of the antithyroglobulin antibodies suggests a significant statistical increase of their level in the whole research sample (in both men and women).

The results of aTSHR level in the research sample are shown in Figure 8. The upper norm limit (aTSHR = 2 IU/ml) was marked with a thick line. The overall data of the increased aTSHR level are presented in Table X.

**Table VIII.** Percentage rate of increased aTPO level with division into sexes among the research sample**Tabela VIII.** Rozkład procentowy zwiększonych stężeń aTPO z podziałem na płeć u pacjentów z grupy kontrolnej

	Male		Female	
	aTPO > 60 IU/ml Doubtful and positive	aTPO > 100 IU/ml Positive	aTPO > 60 IU/ml Doubtful and positive	aTPO > 100 IU/ml Positive
Research sample	2 (5.13%)	2 (5.13%)	9 (14.29%)	9 (14.29%)

**Fig. 7.** Quantitative rate of aTG level with division into sexes among the research sample**Ryc. 7.** Rozkład ilościowy stężeń aTG z podziałem na płeć u pacjentów z grupy kontrolnej

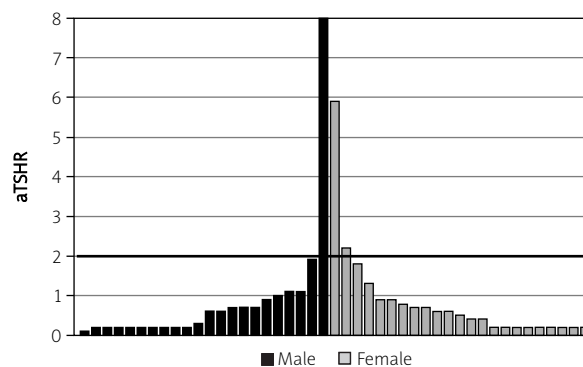
The above analysis calls attention to the lack of statistically significant frequency of occurrence of increased level of antireceptor antibodies in the whole research sample (in both men and women).

## Discussion

The analysis of the research points out the statistically significant increased possibility of disorders of thyroid gland function in patients with Crohn's disease. The observed increased and statistically significant percentage of antithyroid antibodies aTG or aTPO, or both at the same time, was the same as in the research sample among men and women with Crohn's disease; however, it was different for aTSHR antibodies. Statistically significantly more frequent occurrence of increased TSH levels has been found among the group of men and women with Crohn's disease compared with the research sample. As we know, antithyroid antibodies may have destructive activity in relation to the thyroid gland and, what follows, they may provoke gland function disorders. The evaluation parameter by screening the function of the thyroid gland is TSH. A statistically significant increase of TSH value was observed in the analysed group of women and men with Crohn's disease. There was no statistically significant more frequent occurrence of increased TSH level in the research sample. Perhaps it was related to the

**Table IX.** Percentage rate of increased aTG with division into sexes among the research sample**Tabela IX.** Rozkład procentowy zwiększonych stężeń aTG z podziałem na płeć u pacjentów z grupy kontrolnej

	Male (aTG > 280 IU/ml)	Female (aTG > 280 IU/ml)
Research sample	4 (10.26%)	9 (14.29%)

**Fig. 8.** Quantitative rate of aTSHR level with division into sexes among the research sample**Ryc. 8.** Rozkład ilościowy stężeń aTSHR z podziałem na płeć u pacjentów z grupy kontrolnej**Table X.** Percentage rate of increased aTSHR level with division into sexes among the research sample**Tabela X.** Rozkład procentowy zwiększonych stężeń aTSHR z podziałem na płeć u pacjentów z grupy kontrolnej

	Male (TSHR > 2 IU/ml)	Female (TSHR > 2 IU/ml)
Research sample	1 (2.56%)	2 (3.17%)

development of the second autoimmune disease (statistically significantly increased frequency of aTSHR antibody levels) or to problems with absorption of iodine, which is the substrate in thyroid hormone production. The increased TSH levels in most cases is connected with hypothyroidism. Overt or even subclinical

hypothyroidism can be related to slower metabolism among patients. Hypothyroidism in children results in failure to thrive, and in adults leads to weight gain, drowsiness, retardation, problems with memory, lower exercise tolerance and lower intellectual performance. The arterial pressure shows increased systolic and diastolic amplitude; however, in 20% of cases hypertension, mainly of diastolic character, may develop. Menstruation disorders, problems with conceiving and pregnancy course may occur in women with thyroid gland function disorders. Lowered libido and erection disorders are observed in men. In some patients the hypothyroidism can be hidden under the mask of depressive disorders. Anaemia and lipid balance disorders are revealed in the laboratory tests. Anaemia is associated with decreased haemoglobin concentration related to thyroxin deficiency and iron absorption disorders, B<sub>12</sub> vitamin and folic acid. What is more, increased iron loss may occur in women with menorrhoea. Lipid balance disorders are characterised by increased levels of total cholesterol, LDL fraction of cholesterol and apolipoprotein B and triglycerides in serum. Hypothyroidism constitutes a serious health problem for the population of patients. On the other hand, Graves-Basedow disease with hyperthyroidism can also disturb function of the digestive tract, e.g. worsen diarrhoea, and disturb function of the circulatory system. Superposition of thyroid gland function symptoms and health effects and symptoms related to the course of Crohn's disease may deteriorate the health state and make the remission of inflammatory intestine disease difficult (e.g. to increase anaemia related to absorption disorders in the course of Crohn's disease) [19]. The problem associated with insufficient diagnosis of coexisting non-specific inflammatory enteritis, among others Crohn's disease, a different autoimmune disease, and the lack of implementation of appropriate treatment of the coexisting disease may result in problems with the remission of the essential disease.

In order to explore the problem we should broaden the research sample to a larger patient population, because the analysis included only a relatively small group of patients. It is difficult to state whether the increased occurrence of TSH > 2.5  $\mu$ IU/ml and TSH > 4.78  $\mu$ IU/ml among the patients with Crohn's disease was related to a higher number of aTSHR antibodies with slackened activity or to iodine absorption disorders. Further research is advisable.

## Conclusions

In patients with Crohn's disease who have problems with diagnosis and treatment, autoimmune thyroid disorder diagnostics is recommended.

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