Polish Annals of Medicine

Journal homepage: https://www.paom.pl

Research paper

Associations between serum levels of thyroid stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3) and clinical symptoms in patients diagnosed with Hashimoto's thyroiditis

Karol Wiśniewski[1], *Monika Bełej*[2], *Joanna Wojtkiewicz*[1]

[1] *Department of Pathophysiology, School of Medicine, Collegium Medicum, University of Wamia and Mazury in Olsztyn, Poland*
[2] *Advanced Materials Engineering and Modelling Group, Faculty of Chemistry, Wroclaw University of Science and Technology, Poland*

Article info

Article history
Received 14 November 2019
Accepted 18 May 2020
Available online 15 October 2020

Keywords
Autoimmune diseases
Symptoms
Hashimoto's thyroiditis
Co-existing diseases

Doi
https://doi.org/10.29089/2020.20.00123

Abstract

Introduction: Hashimoto's thyroiditis (HT), with prevalence of about 0.8%, is one of the most common autoimmune disorders in the world. Due to the fact that HT affects level of thyroid hormones, symptoms of HT are from almost every body system.

Aim: The aim of this study was to estimate the correlations between symptoms reported by patients with HT and the level of TSH, fT3 and fT4 and also to check the frequency of reporting each symptom at presentation and to estimate the frequency of other co-existing with HT autoimmune diseases.

Material and methods: This study included 65 patients with HT who decided to complete the online survey.

Results and discussion: The most common among the reported symptoms were fatigue (77%), sleepiness (60%) and weak concentration (57%). The results also showed higher prevalence of: rheumatoid arthritis, coeliac disease, systemic lupus erythematous, diabetes mellitus type 1, inflammatory bowel disease and atopic dermatitis than in general population. Significant correlations were found between TSH level and the symptoms including: weak concentration ($P = 0.0002$), easy freezing ($P = 0.02$) and body weight gain ($P = 0.02$). There was also a correlation between level of fT3 and physical exercise ($P = 0.02$).

Conclusions: The findings in this study suggest that there is a higher relative risk for some autoimmune disorders (especially rheumatoid arthritis, coeliac disease and systemic lupus erythematous) for people with HT. The findings also suggest that some symptoms of HT correlate with the level of thyroid parameters.

Corresponding author: Joanna Wojtkiewicz, Department of Pathophysiology, School of Medicine, Collegium Medicum, University of Wamia and Mazury in Olsztyn, Warszawska 30, 10-082 Olsztyn, Poland.
E-mail address: joanna.wojtkiewicz@uwm.edu.pl.

1. INTRODUCTION

Hashimoto's thyroiditis (HT), also known as Hashimoto's disease or chronic lymphocytic thyroiditis is now considered to be one of the most common autoimmune disorders in the world. The prevalence of HT is about 0.8%[1] and has still been increasing in the recent years.[2]

Etiology of HT is considered to be multifactorial (Figure 1). The main implicated factors are: anti-thyroid antibodies, T lymphocytes (especially Tregs, and TH17), B lymphocytes, NK cells, expression by thyroid gland human leukocyte antigens (HLA), apoptosis, TNF-related apoptosis-inducing ligand (TRAIL) and bystander activation.[3–5] The two main primary antigens for immune response are thyroperoxidase – an enzyme attached to thyrocyte membrane, which is mainly responsible for transforming I^- to I_2, and thyreoglobulin – a glycoprotein which is a storage form for thyroid hormones in the thyroid follicle.[3] The other antigens which may be implicated in HT are: pendrin – protein which transports I^- into follicular lumen, and Na^+/I^- symporter – which is responsible for transporting I^- into thyrocytes.[6] Beside these immune factors, there are also genetic, environmental and population specific factors.[7] As it comes to the population – women are at least 8 times more likely to be affected than men.[2] There are also reports concerning an increasing prevalence of HT with age and varies with races – highest in the whites, lower in the Mexican Americans, and the lowest in the Afro Americans.[8] Among environmental factors, the most influential ones seem to be the following: smoking, alcohol drinking, selenium, iodine, infections, vitamin D, stress and drugs. What can be surprising is the fact that both smoking and alcohol seem to play a protective role in pathogenesis of HT. As for iodine – people from iodine sufficient countries seems to suffer more often from HT than people who live in Iodine deficient countries.[7] Level of selenium is the next very important factor. Its deficiency is associated with poor immune response[9] and its supplementation can prevent post-partum increase of anti-TPO antibodies and thyroid dysfunction.[10] As far as infection factors are concerned, the most interesting ones seem to be viruses. There is some evidence that Epsteina-Barr virus (EBV)[11] and human herpesvirus 6 (HVV-6)[12] can be involved in pathogenesis of HT. Genetic factors also seem to play an important role in pathogenesis of HT. There is a report which showed that monozygotic twins are more often affected by HT than the dizygotic ones.[13] Among genes – thyroglobulin gene and HLA-DR3 seem to correlate with HT.[7]

Based on etiology, HT can be classified into primary and secondary forms. Primary HT is the most common form of thyroiditis.[2] However, in it one can distinguish six main entities: classic form (peak age at onset: 40–60),[14] fibrous variant (peak age: 60–70), IgG4-related (peak age: 40–50),[15] juvenile form (peak age: 10–18),[16] Hashitoxicosis (peak age: 40–60) and post-partum (peak age: 20–40).[17] Secondary forms of HT are associated with administration of CTLA-4 blocking antibody for solid tumors,[18] cancer vaccines[19] or interferon-alpha for Hepatitis C virus (HCV) infection.[20]

The typical symptoms of HT 2 are presented in Figure 2.

Figure 1. The etiology of HT.

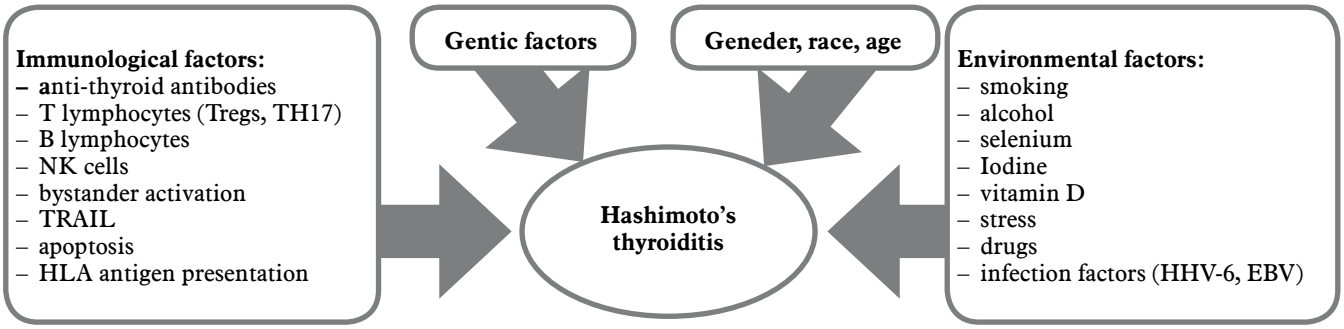
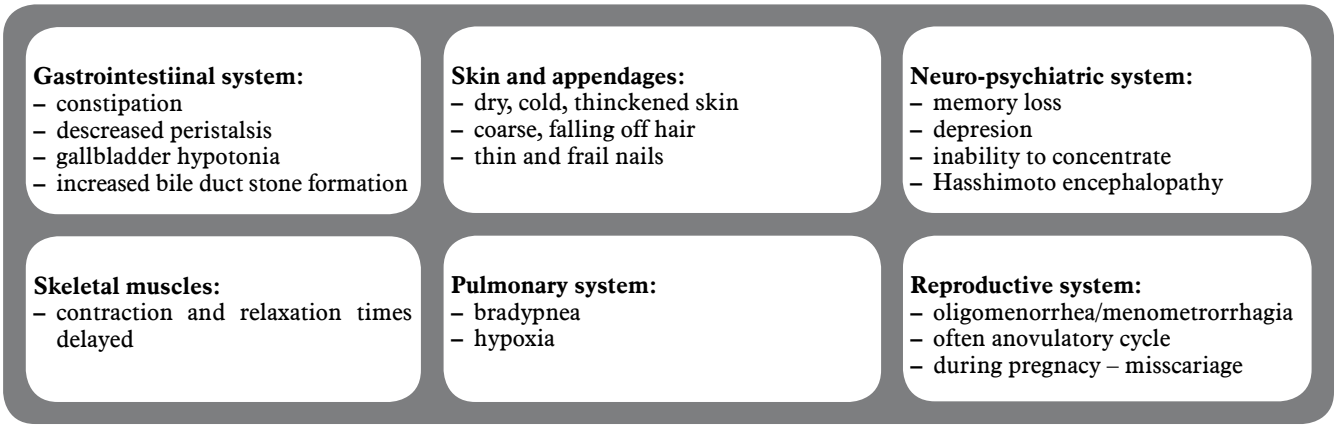


Figure 2. Typical symptoms of HT.



The diagnosis of HT is mainly focused on elevated levels of anty-TPO antibodies or anty-Tg antibodies and goiter or atrophic thyroid and/or hypothyroidism. The HT can also be diagnosed by cytological examination of thyroid aspirate. Other clinical examination tools used in diagnosing HT are USG or scintigraphy.[21]

Currently, there is no rational treatment. Nowadays, therapies are focus on personally dosed, daily, lifelong, oral supplementation of levothyroxine (LT4) in patients with hypothyroidism. In patients with subclinical hypothyroidism the treatment should be given to patients with diabetes, thyroid disorder in past, pregnant women or people with TSH over 10 mIU/L. In other cases, starting treatment is in the discretion of a physician. In case of Hashitoxicosis, treatment with antithyroid agents is not necessary. Other therapies are not currently recommended.[21]

2. AIM

The aim of this study was to estimate the correlation between symptoms reported by patients with HT and the level of TSH, fT3 and fT4. Another objective was to check the frequency of reporting each symptom at presentation and estimate the frequency of co-existing HT with other autoimmune diseases.

2. MATERIAL AND METHODS

This study included 70 patients with HT who decided to complete the online survey. Out of 70 filled questionnaires, 5 were excluded because people who filled them had not tested antibodies (anti-TPO, or anti-Tg). This criterion for exclusion was used because the raised level of anti-TPO or anti-Tg is necessary when diagnosing HT.[21]

The survey consisted of 13 questions concerning: gender, province, how big the city where you are living is, the age of having HT diagnosed, age now, patients' symptoms which caused them to start diagnosing, the starting level of TSH, fT3, fT4, anti-TPO, anti-Tg (all with units), whether there were changes in thyroid USG which are typical for HT, or not and other patient co-existing diseases. All surveys were fully anonymous. The questionnaires were prepared using Google Forms.

To analyse the correlations between patients' symptoms and levels of thyroid parameters, the group of all the patients was divided into three subgroups. First division was based on proper answer to question about first TSH level. From 65 analysed questionnaires, 9 were excluded – because of not being answered, or because of too big, improper TSH value (for example – 345mIU/L). The level of excluding was set at 25 mIU/L. The second division was based on proper answer to question about first fT3 level. From 65 patients, 40 were excluded – because of not entering fT3 level or the unit (of fT3 level). The third division was based on proper answer to question about first fT4 level – here 27 patients were included, the others were excluded because of not entering fT4 level or the unit (of fT4 level). Because of the fact that some patients had their fT3 results in pmol/L and others in pg/mL, all the values reported in pg/mL were converted into pmol/L (1 pg/mL = 1.5361 pmol/L). A similar problem concerned fT4 levels – there were patients with fT4 levels expressed in pmol/L and others with values in ng/dL. Therefore, all the values reported in ng/dL were converted into pmol/L (1 ng/dL = 12.8720 pmol/L).

In each subgroup we checked correlation between every included in survey symptom (body weight gain, weakness, fatigue, sleepiness, weak concentration, worse toleration of physical exercise, oedema, easy freezing, dry-cold-pale skin, dry-brittle hair, low blood pressure, hoarseness, menstrual disorders, constipation, overall bad feeling, there were no symptoms – routine control made by a doctor, there were no symptoms – routine control made by oneself and the level of thyroid parameters (TSH level, fT3 level, fT4 level). All statistical analyses were performed with the use of Statistica v. 13.3. The *U* Mann-Whitney test was used to calculate statistical significance between each symptom and thyroid parameters. The *P* value of less than 0.05 was considered to indicate statistical significance.

3. RESULTS

3.1. General information:

In this study, 65 patients took part – 61 women (94%) and 4 men (6%). Most of them (40%, $n = 26$) lived in cities with over 100 000 residents, 20% ($n = 13$) in cities with 50 001–100 000 residents, 23% ($n = 15$) in cities with 5000–50 000 residents, and 17% ($n = 11$) in cities with lower than 5000 residents. Most of the participants (42%, $n = 27$) were in age between 30–39 years old, 22% ($n = 14$) were 40–49 years old, 23% were in age of 20–29 years old, 11% ($n = 7$) were over 50 years old, and 3% ($n = 2$) were younger than 20 years old.

When it comes to the age of diagnosing HT, most of the interviewees were then in age of 30–39 years old (40%, $n = 26$). Next 32% ($n = 21$) were between 21–29, 9% ($n = 6$) were between 10–19, 9% ($n = 6$) were between 40–49, 5% ($n = 3$) were between 50–59, 3% ($n = 2$) were over 60, and 2% ($n = 1$) of patients was in age lower than 10 years.

3.2. USG changes

In this study, 87.7% ($n = 57$) of the patients had changes in thyroid USG, which were characteristic for HT, 7.7% ($n = 5$) had no characteristic changes, and 4.6% ($n = 3$) had no examined thyroid by USG.

Co-existing diseases of patients who were included in this study are presented in Table 1.

3.3. Symptoms

The symptom, which was reported by patients most often, was fatigue – with over 75% of patients suffering from it. The second most reported symptom was sleepiness (60%), and the third one was weak concentration (57%). Over 50% of partici-

pants suffered also from: body weight gain (55%), weakness (55%), easy freezing (51%) and overall bad feeling (51%). In this study, patients reported dry, brittle hair (48%), dry, cold, pale skin (43%), worse toleration of physical exercise (40%), menstrual disorders (35%; 38% of women), constipation (26%), low blood pressure (25%), oedema (20%)and hoarseness (12%). What is really interesting is that 6% of patients had no symptoms at the moment of starting diagnosing – half of them discovered the disease during a routine examination conducted by a doctor and the other half during a routine examination conducted by themselves (Figure 3).

Table 1. Co-existing diseases.

Co-existing diseases	Number of patients, *n*(%)
Allergies	20(30.77)
PCOS	5(7.69)
Diabetes mellitus type 2	4(6.15)
RA	4(6.15)
AD	4(6.15)
Hypertension	3(4.62)
Arteriosclerosis/ hyperlipidaemia	3(4.62)
IBD	3(4.62)
Asthma	3(4.62)
Diabetes mellitus type 1	1(1.54)
Coeliac disease	1(1.54)
SLE	1(1.54)
No other diseases	25(38.46)

3.4. Correlation between thyroid parameters and symptoms

As far as TSH and the symptoms reported by patients at presentation are concerned, a significant correlation between TSH and: weak concentration ($P = 0.0002$), easy freezing ($P = 0.02$) and body weight gain ($P = 0.02$) was observed.There was also observed a tendency ($P < 0.1$) between TSH and worse toleration of physical exercise ($P = 0.06$) (Table 2). In other symptoms there was seen no correlation or tendency ($P > 0.1$).

Between fT3 and reported symptoms there was observed one correlation – between worse toleration of physical exercise ($P = 0.02$) (Table 2). Between other symptoms there was seen no correlation or tendency ($P > 0.1$).

Between fT4 and reported by participants symptoms there was seen no correlation or tendency ($P > 0.1$) .

4. DISCUSSION

In the study, 65 patients took part – 61 women (94%) and 4 men (6%), which represented the general trend that women are affected with HT more often than men.[2] The most patients (65%, $n = 42$) were 20–39 years old and only 32% ($n = 21$) patients were over 40 years old. However other reports pointed out that the prevalence of HT is increasing with

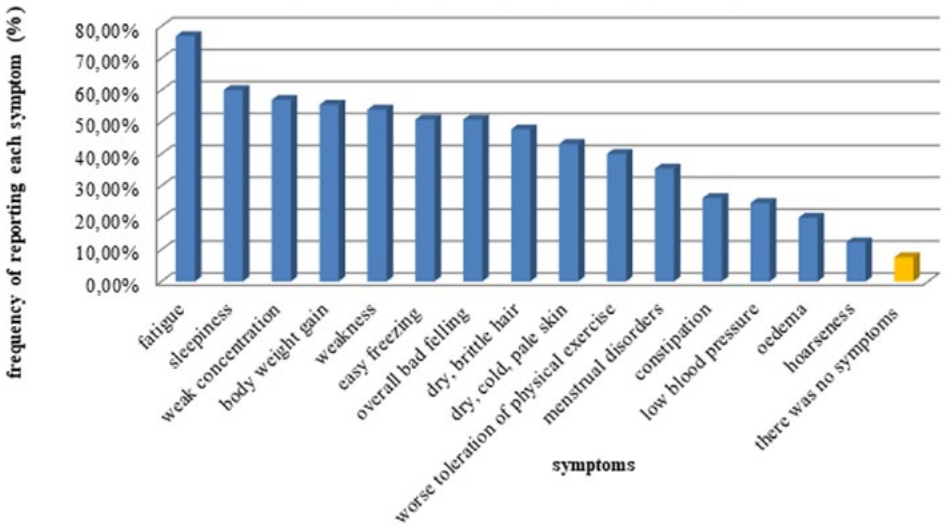


Figure 3. Frequency of reporting each symptoms by patients.

Table 2. Correlations between thyroid parameters and present of chosen symptoms ($P < 0.1$).

Thyroid parameter	Symptoms	Symptom not present	Symptom present	*P*
TSH	body weight gain	4.0(2.5–7.5)	6.0(4.7–9.0)	0.02
	weak concentration	3.8(2.5–5.6)	6.6(5.3–9.2)	0.0002
	easy freezing	4.3(2.4–6.0)	6.0(4.7–8.5)	0.02
	worse toleration of physical exercise	4.9(2.5–7.1)	6.0(4.5–10.0)	0.06
fT3	worse toleration of physical exercise	4.6(4.1–5.4)	5.3(5.1–5.9)	0.02

Comments: Level of TSH is given in mIU/L unit and fT3 in pmol/L. All numbers are presented as median(IQR).

age.[8] The authors of the study assume that the population included in the study does not represent this tendency, due to fact that the data was collected by online surveys – so younger patients rather than the older respondents were more likely to send their questionnaires.

When it comes to USG changes – 62 patients included in the study had thyroid USG, from whom 92% (n = 57) have USG changes suggesting HT. These results are also in agreement with other studies showing high sensitivity and specificity of USG in diagnosing or determine therapeutic efficiency.[22–24] Nowadays, more and more efforts are put in computer-aided diagnostic (CAD), which relying on greyscale features can provide objective differentiation between HT and healthy patients. This technique has a sensitivity of 84.6%, specificity of 87.0 % and a positive predictive value of 88.9%,[25] which shows how valuable a tool it can be for a clinical use.

From 65 patients included in the study, over 60% (n = 40) had some kind of co-existing disease. The most common one included allergies (31%). It is not a surprise, because over 25% of population is suffering from allergy of some kind,[26] but such big frequency of allergies can prove some kind of immunology disorders in patients with HT.

The second most common co-existing disease was polycystic ovary syndrome (PCOS) – with 8% of women suffering from it. The prevalence of PCOS worldwide is 6%–21%, so the results obtained in this study have not shown that women with HT suffered more often from PCOS than general population. However, there are many reports that prevalence of HT is higher in PCOS patients – 22.1%–27% vs. 5%–8% (PCOS and general population respectively).[27,28]

In this study 6.2% of patients included in the study also suffered from rheumatoid arthritis (RA), which is much more often than the prevalence of RA in general population (0.55%).[29] This result is in agreement with other big study in which RA affected 4.24% people with HT.[29]

The results obtained in the study also suggest higher prevalence of coeliac disease and systemic lupus erythematosus (SLE) in people with HT than in general population (1.5% vs. 0.05% and 1.5% vs. 0.027%,[29] respectively). Here, the results are in agreement with other studies.[29,30] It is also worth mentioning that HT prevalence in SLE patients is also higher than in controls.[31]

In this study, the prevalence of inflammatory bowel disease (IBD) in patients with HT vs. general population (4.6% vs. 0.26%[29]). This result is in the contrary to other study, which showed no such tendency in bigger population.[29] It is also worth mentioning that from other studies it does not seem that patients with IBD will be more often affected by HT than the general population.[32]

When it comes to diabetes mellitus type 1, there was also a bit higher prevalence than in general population (1.5% vs. 0.34%) observed. This result is also in the contrary to other study.[29]

The results of the study also showed higher prevalence of AD than in general population (6.2% vs. 3.9%[33]). The prevalence of asthma was not different than in general population (4.6% vs. 2%–6%[34] respectively).

From the obtained results, it seems that the prevalence of diabetes mellitus type 2 (6.2% vs. 6.7%–7%[35]), hypertension (4.6% vs. 68%–72%[36]) and arteriosclerosis/hyperlipidemia (4.6% vs. 67%[37]) was lower than in general population. These results may be conditioned on the fact that the young female population (mainly 20–40 years old) was included in the study and the prevalence of these diseases increases with age and is also higher in men. Further studies on older population should be more representative in evaluation of relative risk of these disorders in patients with HT.

The three most frequently reported symptoms by patients included: fatigue (77%), sleepiness (60%) and weak concentration (57%). Other symptoms which were reported by over half of interviewees were: body weight gain (55%), weakness (54%), easy freezing (51%) and overall bad feeling (51%). What is worth mentioning is the fact that 40% of all patients has a triad of three most common symptoms: fatigue, sleepiness and weak concentration. These results are different from other study, which showed that the most common complaint at presentation included swelling in the neck (58%), nervousness (18%), dermatological problems (13%) and hair loss (8%).[38] In the study, dry and cold and pale skin was reported by 43% and dry and brittle hair by 48%, nervousness or swelling in the neck was not reported. Both studies were conducted on similar groups (65 vs. 101), but the other study was focused on children and adolescent under 18 years old, whereas this study focused mainly on 20–40 years old. This difference can be responsible for different symptoms at presentation.

This study also showed that some symptoms of HT correlated with the level of thyroid parameters. Weak concentration, body weight gain and easy freezing correlated with TSH level and worse toleration of physical exercise correlated with fT3 level. Among other symptoms, there were no other correlations ($P > 0.05$) seen.

5. CONCLUSIONS

The results obtained in this study showed that there is an increased risk for co-existing autoimmune disorders for patients with HT (especially for RA, coeliac disease and SLE). Having this knowledge, the authors of this study, as well as other authors, support the idea of routine screening of the patients with HT for these disorders. The results obtained from this study showed that the most common occurring symptoms are fatigue, sleepiness and weak concentration. This fact leads to the conclusion that every woman who reports these symptoms should be screened for HT. This study also showed that there are some correlations between symptoms reported by patients and levels of thyroid parameters. Further studies in this area carried on larger groups are needed.

Conflict of interest
None declared.

Funding
None declared.

Ethics
The study protocol was approved by the local Bioethics Committee (No 34/2019).

References
1 Jenkins RC, Weetman AP. Disease associations with autoimmune thyroid disease. *Thyroid*. 2002;12(11):977–988. https://doi.org/10.1089/105072502320908312.
2 Caturegli P, Remigis AD, Rose N. Hashimoto thyroiditis: Clinical and diagnostic criteria. *Autoimmun Rev*. 2014;13 (4–5):391–397. https://doi.org/10.1016/j.autrev.2014.01.007.
3 Berghi N. Immunological mechanisms implicated in the pathogenesis of chronic urticaria and Hashimoto thyroiditis. *Iran J Allergy Asthma Immunol*. 2017;16(4):358–366.
4 Pyzik A, Grywalska E, Matyjaszek-Matuszek B, Roliński J. Immune disorders in Hashimoto's thyroiditis: What do we know so far? *J Immunol Res*. 2015;2015:1–8. https://doi.org/10.1155/2015/979167.
5 Popko K, Górska E. The role of natural killer cells in pathogenesis of autoimmune diseases. *Cent Eur J Immunol*. 2015;40(4):470–476. https://doi.org/10.5114/ceji.2015.56971.
6 Czarnocka B. Thyroperoxidase, thyroglobulin, Na^+/I^- symporter, pendrin in thyroid autoimmunity. *Front Biosci*. 2011;16(1):783–802. https://doi.org/10.2741/3720.
7 Dong YH, Fu DG. Autoimmune thyroid disease: mechanism, genetics and current knowledge. *Eur Rev Med Pharmacol Sci*. 2014;18(23):3611–3618.
8 Mcleod DSA, Cooper DS. The incidence and prevalence of thyroid autoimmunity. *Endocrine*. 2012;42(2):252–265. https://doi.org/10.1007/s12020-012-9703-2.
9 Schomburg L. Selenium, selenoproteins and the thyroid gland: interactions in health and disease. *Nat Rev Endocrinol*. 2011;8(3):160–171. https://doi.org/10.1038/nrendo.2011.174.
10 Negro R, Greco G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. The influence of selenium supplementation on postpartum thyroid status in pregnant women with thyroid peroxidase autoantibodies. *J Clin Endocrinol Metab*. 2007;92(4):1263–1268. https://doi.org/10.1210/jc.2006-1821.
11 Janegova A, Janega P, Rychly B, Kuracinova K, Babal P. The role of Epstein-Barr virus infection in the development of autoimmune thyroid diseases. *Endokrynol Pol*. 2015;66(2):132–136. https://doi.org/10.5603/ep.2015.0020.
12 Caselli E, Zatelli MC, Rizzo R, et al. Virologic and immunologic evidence supporting an association between HHV-6 and Hashimotos thyroiditis. *PLoS Pathogens*. 2012;8(10): e1002951. https://dx.doi.org/10.1371%2Fjournal.ppat.1002951.
13 Brix TH. A population-based study of chronic autoimmune hypothyroidism in Danish twins. *J Clin Endocrinol Metab*. 2000;85(2):536–539. https://doi.org/10.1210/jcem.85.2.6385.
14 Caturegli P, Remigis AD, Chuang K, Dembele M, Iwama A, Iwama S. Hashimotos thyroiditis: Celebrating the centennial through the lens of the Johns Hopkins hospital surgical pathology records. *Thyroid*. 2013;23(2):142–150. https://doi.org/10.1089/thy.2012.0554.
15 Li Y, Bai Y, Liu Z, et al. Immunohistochemistry of IgG4 can help subclassify Hashimoto's autoimmune thyroiditis. *Pathol Int*. 2009;59(9):636–641. https://doi.org/10.1111/j.1440-1827.2009.02419.x.
16 Luca FD, Santucci S, Corica D, Pitrolo E, Romeo M, Aversa T. Hashimoto's thyroiditis in childhood: presentation modes and evolution over time. *Riv Ital Pediatr*. 2013;39(1):8. https://dx.doi.org/10.1186%2F1824-7288-39-8.
17 Stagnaro-Green A. Approach to the patient with postpartum thyroiditis. *J Clin Endocrinol Metab*. 2012;97(2):334–342. https://doi.org/10.1210/jc.2011-2576.
18 Corsello SM, Barnabei A, Marchetti P, Vecchis LD, Salvatori R, Torino F. Endocrine side effects induced by immune checkpoint inhibitors. *J Clin Endocrinol Metab*. 2013;98(4):1361–1375. https://doi.org/10.1210/jc.2012-4075.
19 Vita R, Guarneri F, Agah R, Benvenga S. Autoimmune thyroid disease elicited by NY-ESO-1 vaccination. *Thyroid*. 2014;24(2): 390–394. https://dx.doi.org/10.1089%2Fthy.2013.0170.
20 Mandac JC, Chaudhry S, Sherman KE, Tomer Y. The clinical and physiological spectrum of interferon-alpha induced thyroiditis: Toward a new classification. *Hepatology*. 2006;43(4):661–672. https://doi.org/10.1002/hep.21146.
21 Radetti G. Clinical aspects of Hashimoto's thyroiditis. In: Szinnai G, ed. *Paediatric Thyroidology*. Basel: Karger. 2014;26:158–170. https://doi.org/10.1159/000363162.
22 Wu G. Ultrasonography in diagnosis of Hashimoto's thyroiditis. *Front Biosci (Landmark Ed)*. 2016;21:1006–1012. https://doi.org/10.2741/4437.
23 Reinhardt W, Luster M, Rudorff K, et al. Effect of small doses of iodine on thyroid function in patients with Hashimoto's thyroiditis residing in an area of mild iodine deficiency. *Eur J Endocrinol*. 1998;139:23–28. https://doi.org/10.1530/eje.0.1390023.
24 Tajiri J. Radioactive iodine therapy for goitrous Hashimoto's thyroiditis. *J Clin Endocrinol Metab*. 2006;91(11):4497–4500. https://doi.org/10.1210/jc.2006-1163.
25 Acharya UR, Sree SV, Krishnan MMR, et al. Computer-aided diagnostic system for detection of Hashimoto thyroiditis on ultrasound images from a Polish population. *J Ultrasound Med*. 2014;33(2):245–253. https://doi.org/10.7863/ultra.33.2.245.
26 Bousquet J, Schunemann HJ, Fonseca J, et al. MACVIA-ARIA Sentinel NetworK for allergic rhinitis (MASK-rhinitis): The new generation guideline implementation. *Allergy*. 2015;70(11):1372–1392. doi:10.1111/all.12686
27 Arduc A, Dogan BA, Bilmez S, et al. High prevalence of Hashimoto's thyroiditis in patients with polycystic ovary syndrome: Does the imbalance between estradiol and progesterone play a role? *Endocr Res*. 2015;40(4):204–210. https://doi.org/10.3109/07435800.2015.1015730.
28 Kowalczyk K, Franik G, Kowalczyk D, Pluta D, Blukacz Ł, Madej P. Thyroid disorders in polycystic ovary syndrome. *Eur Rev Med Pharmacol Sci*. 2017;21(2):346–360.
29 Boelaert K, Newby PR, Simmonds MJ, et al. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. *Am J Med*. 2010;123(2):183. e1–9. https://doi.org/10.1016/j.amjmed.2009.06.030.
30 Tuhan H, Işık S, Abacı A, et al. Celiac disease in children and adolescents with Hashimoto thyroiditis. *Turk Pediatri Ars*. 2016;51(2):100–105. https://dx.doi.org/10.5152%2FTurkPediatriArs.2016.3566.

[31] Posselt RT, Coelho VN, Skare TL. Hashimoto thyroiditis, anti-thyroid antibodies and systemic lupus erythematosus. *Int J Rheum Dis*. 2017;21(1):186–193. https://doi.org/10.1111/1756-185x.13089.

[32] Shizuma T. Concomitant thyroid disorders and inflammatory bowel disease: A literature review. *Biomed Res Int*. 2016;2016:5187061. https://doi.org/10.1155/2016/5187061.

[33] Sybilski AJ, Raciborski F, Lipiec A, et al. Epidemiology of atopic dermatitis in Poland according to the Epidemiology of Allergic Disorders in Poland (ECAP) study. *J Dermatol*. 2014;42(2):140–147. https://doi.org/10.1111/1346-8138.12731.

[34] Zalewska M, Furmańczyk K, Jaworski S, Niemiro W, Samoliński B. The prevalence of asthma and declared asthma in Poland on the basis of ECAP survey using correspondence analysis. *Comput Math Methods Med*. 2013;2013:597845. https://dx.doi.org/10.1155%2F2013%2F597845.

[35] Rutkowski M, Bandosz P, Czupryniak L, et al. Prevalence of diabetes and impaired fasting glucose in Poland – the NATPOL 2011 Study. *Diabet Med*. 2014;31(12):1568–1571. https://doi.org/10.1111/dme.12542.

[36] Kearney PM, Whelton M, Reynolds K, Whelton PK, He J. Worldwide prevalence of hypertension: A systematic review. *J Hypertens*. 2004;22(1):11–19. https://doi.org/10.1097/00004872-200401000-00003.

[37] Niklas A, Flotyńska A, Puch-Walczak A, et al. Prevalence, awareness, treatment and control of hypertension in the adult Polish population – Multi-center National Population Health Examination Surveys – WOBASZ studies. *Arch Med Sci*. 2018;14(5):951–961. https://doi.org/10.5114/aoms.2017.72423.

[38] Özen S, Berk Ö, Şimşek DG, Darcan S. Clinical course of Hashimoto's thyroiditis and effects of levothyroxine therapy on the clinical course of the disease in children and adolescents. *J Clin Res Pediatr Endocrinol*. 2011;3(4):192–197. https://dx.doi.org/10.4274%2Fjcrpe.425.