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A preliminary assessment of the impact of women's susceptibility to Hashimoto's thyroiditis on the occurrence of anxiety and depressive disorders

Katarzyna Karakiewicz-Krawczyk, Anna Knyszyńska, Sylwia Wieder-Huszla, Paulina Zabielska, Joanna Włodarska, Anna Jurczak

Abstract

Aim: There huge differences in the incidence of autoimmune thyroid diseases between women and men, which is caused by sexual differentiation of the immune system. Hashimoto's thyroiditis is now one of the most prevalent autoimmune disorders. Its diagnosis is challenging, and its effects on mental health can often impose a greater burden on the patients than physical symptoms. The aim of this study was to make a preliminary assessment of anxiety levels and depressive symptoms in women with diagnosed Hashimoto's disease.

Material and methods: The study included 205 women with Hashimoto's thyroiditis. The study consisted of two parts. Part one employed the diagnostic survey method with the use of standardized questionnaires and a proprietary interview questionnaire. Part two involved the analysis of biochemistry parameters in blood serum to determine thyroid status.

Results: The analysis revealed moderate anxiety levels in women with Hashimoto's disease. Women with moderate and severe depression were in the minority, while mild depression was observed in 40% of the participants. A statistically significant relationship was demonstrated between state anxiety and TSH level.

Discussion: Patients with autoimmune thyroiditis are at risk for the development of depression, social phobia, anxiety disorders and sleep disorders.

Conclusions: Depressive symptoms co-occur with anxiety disorders in the group of women with Hashimoto's thyroiditis. The studied group of patients presented mild depressive symptoms and moderate anxiety disorders. A higher level of state anxiety in the group of women with Hashimoto's disease is correlated with higher serum TSH. Lower serum FT4 co-occurs with more severe symptoms of depression and anxiety.

depressive disorder; anxiety; Hashimoto's disease; hypothyroidism

Katarzyna Karakiewicz-Krawczyk[1], Anna Knyszyńska[2], Sylwia Wieder-Huszla[1], Paulina Zabielska[3], Joanna Włodarska[3], Anna Jurczak[1]: [1]Department of Clinical Nursing, Pomeranian Medical University in Szczecin, Szczecin, Poland; [2]Department of Functional Diagnostics and Physical Medicine, Pomeranian Medical University in Szczecin, Szczecin, Poland; [3]Subdepartment of Social Medicine and Public Health, Department of Social Medicine, Pomeranian Medical University in Szczecin, Szczecin, Poland.
Correspondence address: paulina.zabielska@pum.edu.pl

INTRODUCTION

Hashimoto's disease is also known as chronic autoimmune thyroiditis, or chronic lymphocytic thyroiditis, resulting from lymphocytic infiltration of the thyroid parenchyma [1,2]. Hashimo-

to's thyroiditis (HT) was described over a hundred years ago as a marked lymphoid goitre affecting predominantly women. Apart from the classic form, the term covers several other clinical pathological entities: the fibrous variant, IgG4-related thyroiditis, juvenile form, Hashitoxicosis and painless (silent) thyroiditis. All variants are characterised by pathological infiltration of hematopoietic mononuclear cells, mainly lymphocytes. Thyroid cells undergo atrophy or transform into a more distinct type of follicular cell rich in mitochondria, called Hürthle cells [3]. Most HT forms ultimately evolve into hypothyroidism of varying severity, but some patients may present euthyroid with normal concentrations of TSH and thyroid hormones, T3 and T4. In rare cases, Hashimoto's disease may present with an overactive thyroid (hyperthyroidism) [3].

Hashimoto's disease is regarded as one of the most prevalent chronic conditions of autoimmune origin, observed predominantly in women, with the mean annual incidence among women amounting to 3.5 per 1000, compared to 0.8 per 1000 in men. The higher prevalence in women suggests that oestrogens may be involved in the pathogenesis of the disease, which seems to be confirmed by the highest number of new cases observed during puberty, pregnancy and menopause. The odds of developing Hashimoto's disease go up with age, with peak incidence observed in the age range 45–65 years [3, 4, 5]. Genetic factors are also believed to be implicated in the development of the disease, with 50% of first-degree relatives of HT patients presenting elevated serum levels of antithyroid antibodies [6].

The clinical features of HT include both local manifestations, i.e. dysphonia, dyspnoea and dysphagia, related to the compression caused by the enlarged thyroid gland on the neighbouring neck structures, and systemic symptoms arising as a result of endocrine dysfunction of the gland itself. Seen as thyroid hormones have a profound effect on most of the body's organs and organ systems, these symptoms can be numerous and varied. Symptoms may involve the gastrointestinal tract, renal, respiratory, and circulatory systems, skeletal muscles, skin and neuro-psychiatric disorders [3].

The profound impact of HT on psychological functioning is increasingly recognized. Mental health symptoms in the form of depressive disorders or irritability often precede the full-blown clinical manifestation of the disease [7]. Some HT patients experience apathy, lethargy, slowing of speech and reflexes. These symptoms may be accompanied by a depressed mood, anxiety, depressive disorders or even psychosis [7, 8]. Some scholars suggest that patients with hypothyroidism have symptoms very much like those of affective disorders [9, 10]. The relationship between thyroid disease and depression has been the subject of study since the 1960s, butnofirm conclusions have been reached in this scope. Studies into the correlations between untreated and/or diagnosed hypothyroidism and depression/anxiety are undertaken by numerous independent research teams [11, 12, 13].The aim of this study was to make a preliminary assessment of anxiety levels and depressive symptoms in women with diagnosed Hashimoto's disease.

MATERIALS AND METHODS

The study was conducted in a group of 205 women with Hashimoto's thyroiditis who were patients of an endocrine clinic. Each participant was given information about the aim and procedure of the study with a written assurance that she can withdraw from the study at any stage of the research process, without having to explain the reasons for the decision. Patients had to give informed consent to be included in the study. The study was approved by the Bioethics Committee of the Pomeranian Medical University (Resolution no KB-0012/135/18). The study consisted of two parts. Part one employed the diagnostic survey method with the use of two standardized instruments, i.e. the STAI Questionnaire and Beck Depression Inventory, while part two was based on the analysis of blood serum biochemistry. According to the research protocol, after obtaining informed consent from each of the eligible women, a single sample of up to 5.5 ml venous blood was collected after an overnight fast (at least 8 hours since the last meal) using a Monovette closed system for the purposes of determining blood serum parameters of thyroid hormones: TSH (normal range: 0.27–4.20 μIU/ml (0.27–4.20 μIUmL-1)) and FT4 (normal range: 0.93–1.70 ng/dl(9.3–17.0 ng L-1)).

The rates of anxiety among the studied women were assessed using the State-Trait Anxiety Inventory (STAI), developed by C.D. Spielberger, R.L. Gorsuch, R.E. Lushene. The Inventory consists of two subscales, intended to measure anxiety understood as a temporary and situation-specific state of the individual (X-1), and anxiety understood as a relatively stable part of one's personality (X-2). The answers are scored according to appropriate rating scales, and added up to produce the raw score, which is then converted to a standardized sten score. Sten scores in the range 1–4 may be regarded as corresponding to allow anxiety level, 5–6 indicate a moderate form of anxiety, while sten scores of 7–10 – a severe form of anxiety [14]. The other instrument used in the study was the Beck Depression Inventory (BDI-II), which provides information on the presence and severity of depressive symptoms. Based on the scores from the Inventory,it is possible to determine the absence of depression (0–11), or the presence of mild (12–26), moderate (27–49) or severe depression (50–63) [15]. Personal data were collected using a proprietary questionnaire survey, aided by an analysis of the available medical records.

Statistical analysis was performed using the R software package, version 3.5.0. The results were analysed using descriptive statistics, including the number of valid cases, arithmetic mean, standard deviation, median, minimum, maximum. Analysis also included stratum weights and mathematical statistics, like fit of distribution testing, non-parametric correlations and tests of significance. It was assumed that probability $p \leq 0.05$ is statistically significant, and $p \leq 0.01$ is highly significant.

RESULTS

The age of the women included in study ranged from 19 to 72 years. The mean age was 44 years (SD=11.41). The mean values of analyzed blood parameters amounted to 2.75±3.03 for TSH, and 1.31 ±0.24 for FT4. Both state and trait anxiety averaged at the moderate level. In terms of the mean BDI-II score (12 pts), the study group was characterized by mild depression (Table 1).

Table 1. Means and medians of blood biochemistry and survey results

Variable		Study group n=205			
		Min-Max	M±SD	Me	Q1-Q3
age [years]		19-72	44±11.41	43	37-52
Thyroid hormone levels	TSH [μIU/ml]	0.02-32	2.75±3.03	2.20	1.37-3.30
	FT4 [ng/dl]	0.72-2.42	1.31±0.24	1.28	1.17-1.45
State anxiety	STAI – I [sten]	1-10	6±1.96	6	5-7
Trait anxiety	STAI – II [sten]	1-7	5.9±2.08	6	4-7
Depression	BDI – II [pts]	0-50	14±10.19	12	6-20

n — number; % — percentage; FT4 — free thyroxine; TSH — thyroid stimulating hormone; M — mean; SD — standard deviation; Q1 — first quartile; Q3 — third quartile

For a significant majority of the participants, the values of analysed thyroid hormones fell into the reference range. Yet, 46 TSH results and 22 FT4 results were outside the normal range (Table 2).

Table 2. Distribution of TSH and FT4 levels in the studied group of women

	TSH		
	low <0.27 μIU/mL (<0.27 μIUmL^{-1})	normal 0.27-4.20 μIU/mL (0.27-4.20 μIUmL^{-1})	high >4.20 μIU/mL (>4.20 μIUmL^{-1})

n	14	159	32
%	6.8	77.6	15.6
	FT4		
	low <0.93 ng/dl (<9.3 ng L^{-1})	normal 0.93–1.70 ng/dl (9.3–17.0 ng L^{-1})	high >1.70 ng/dl (>17.0 ng L^{-1})
n	10	183	12
%	4.9	89.3	5.9

n — number; % — percentage; FT4 — free thyroxine; TSH — thyroid stimulating hormone;

Data analysis revealed a moderate level of state anxiety in nearly 40% of the studied women, while at the same time 40% presented a high level of trait anxiety. For 23.9% and 25.4% of the participants, anxiety on the state and trait subscales respectivelyfell in the low range. More than half of the women with Hashimoto's thyroiditis (51.2%) presented depressive symptoms of varying severity, most frequently in the mild form (40%), while severe depression was observed only in one participant. Almost half, i.e. 48.8% of women, showed no signs of depression (Table 3).

Table 3. Analysis of severity of anxiety and depressive symptoms in the studied group of women

		Study group (n=205)	
		n	%
state anxiety level STAI – I	low	49	23.9
	moderate	81	39.5
	high	75	36.6
trait anxiety level STAI – II	low	52	25.4
	moderate	71	34.6
	high	82	40
severity of depression BDI-II	no depression	100	48.8
	mild	82	40.0
	moderate	22	10.7
	severe	1	0.5

The majority of participants who had normal levels of the thyroid stimulating hormone (TSH) were women without symptoms of depression – 40% (82). On the other hand, the number of women presenting symptoms of depression of varying severity (from mild to severe) whose TSH was in the reference range was not much smaller – 37.6% (77). Similar findings were obtained with regard to FT4: 45.4% (93) vs. 37.6% (90). Among women with abnormal (low or high) TSH, depressive symptoms were more common than the absence thereof, affecting 13.6% (28) of the participants compared to 8.8% (11) women with no depression. Likewise, in the analysis of abnormal FT4 levels, 7.3% (15) of the participants presented depressive disorders, mainly in the mild form, while as little as 3.5% (7) showed no symptoms of depression. However, data analysis did not reveal any statistically significant differences in this regard – Table 4.

Table 4. Analysis of severity of depressive symptoms according to thyroid parameters

Thyroid parameters								
TSH								
Severity of depression	Low range		Reference range		High range		$\chi^2_{(df)}$	p
	TSH<0.27 µIU/mL (<0.27 µIUmL^{-1})		TSH 0.27-4.20 µIU/mL (0.27-4.20 µIUmL^{-1})		TSH >4.20 µIU/mL (>4.20 µIUmL^{-1})			
	N	%	N	%	N	%		
No depression	7	3.4	82	40.0	11	5.4	$11.08_{(6)}$	0.086
Mild	7	3.4	61	29.8	14	6.8		
Moderate	0	0.0	16	7.8	6	2.9		
Severe	0	0.0	0	0.0	1	0.5		
FT4								
Severity of depression	FT4<0.93ng/dl (<9.3 ng L^{-1})		FT4 0.93-1.70ng/dl (9.3–17.0 ng L^{-1})		FT4>1.70ng/dl (>17.0 ng L^{-1})		$\chi^2_{(df)}$	p
	N	%	N	%	N	%		
No depression	3	1.5	93	45.4	4	2.0	$6.476_{(6)}$	0.372
Mild	6	2.9	68	33.2	8	3.9		
Moderate	1	0.5	21	10.2	0	0.0		
Severe	0	0.0	1	0.5	0	0.0		

The majority of women whose thyroid parameters were in the normal range showed a moderate level of state anxiety (STAI-1) and a high level of trait anxiety (STAI-2). However, these finding were of no statistical significance –Table 5.

Table 5. Analysis of severity of anxiety according to thyroid parameters

Thyroid parameters								
STAI-1								
STAI-1 anxiety level	Low range		Reference range		High range		$\chi^2_{(df)}$	p
	TSH<0.27 µIU/mL (<0.27 µIUmL^{-1})		TSH 0.27-4.20 µIU/mL (0.27-4.20 µIUmL^{-1})		TSH >4.20 µIU/mL (>4.20 µIUmL^{-1})			
	N	%	N	%	N	%		
Low	4	2.0	39	19	6	2.9	$8.139_{(4)}$	0.087
Moderate	9	4.4	62	30.2	10	4.9		
High	1	0.5	58	28.3	16	7.8		
STAI-1 anxiety level	FT4<0.93ng/dl (<9.3 ng L^{-1})		FT4 0.93-1.70ng/dl (9.3–17.0 ng L^{-1})		FT4>1.70ng/dl (>17.0 ng L^{-1})		$\chi^2_{(df)}$	p
	N	%	N	%	N	%		
Low	2	1.0	44	21.5	3	1.5	$2.243_{(4)}$	0.691
Moderate	3	1.5	72	35.1	6	2.9		
High	5	2.4	67	32.7	3	1.5		
STAI-2								

STAI-2 anxiety level	TSH<0.27 µIU/mL (<0.27 µIUmL^{-1})		TSH 0.27-4.20 µIU/mL (0.27-4.20 µIUmL^{-1})		TSH >4.20 µIU/mL (>4.20 µIUmL^{-1})		$\chi^2_{(df)}$	p
	N	%	N	%	N	%		
Low	5	2.4	41	20	6	2.9	$0.068_{(4)}$	0.185
Moderate	7	3.4	55	26.8	9	4.4		
High	2	1	63	30.7	17	8.3		
STAI-2 anxiety level	FT4<0.93ng/dl (<9.3 ng L^{-1})		FT4 0.93-1.70ng/dl (9.3–17.0 ng L^{-1})		FT4>1.70ng/dl (>17.0 ng L^{-1})		$\chi^2_{(df)}$	p
	N	%	N	%	N	%		
Low	3	1.5	45	22	4	2.0	$3.795_{(4)}$	0.435
Moderate	2	1.0	63	30.7	6	2.9		

Analysis of correlations between the variables revealed that the level of trait anxiety among women with Hashimoto's disease decreased with age. Lower FT4 levels co-occurred with more severe symptoms of anxiety and depression. In turn, TSH levels showed a significant positive correlation only with the level of state anxiety – Table 6.

Table 6. Spearman rank correlations between analyzed variables

	thyroid hormone levels				depression		state anxiety		trait anxiety	
	TSH		FT4		BDI-II		STAI-I		STAI-II	
	rho	p	rho	p	rho	p	rho	p	rho	p
Age	-0.003	0.971	-0.074	0.293	0.125	0.074	-0.073	0.299	-0.232	0.001
STAI-II	0.125	0.074	-0.211	0.002	0.608	0.001	0.648	0.001	-	-
STAI-I	0.177	0.011	-0.139	0.046	0.483	0.001	-	-	-	-
BDI-II	0.129	0.065	-0.242	0.001	-	-	-	-	-	-
FT4	-0.360	0.001	-	-	-	-	-	-	-	-

DISCUSSION

Patients with autoimmune thyroiditis are at risk for the development of depression, social phobia, anxiety disorders and sleep disorders. The high comorbidity between Hashimoto's disease and mood disorders has long been recognized. Both negative mood and other mental disorders result in lower quality of life and generally impaired functioning [7,16, 17]. That is why HT patients, apart from a periodic assessment of thyroid function, should undergo mental health screening, to quickly identify concomitant disorders and, if necessary, implement an appropriate treatment.

The hormones produced by the thyroid gland are essential for the normal function of the nervous system [18]. Among the numerous clinical symptoms of Hashimoto's thyroiditis related to the entire spectrum of endocrine dysfunction of the thyroid gland (from hyperthyroidism, subclinical hypothyroidism to full-blown hypothyroidism), neuro-psychiatric symptoms form a distinct category [16]. Psychiatric symptoms most commonly associated with endocrine abnormalities include mood disorders, reduced concentration, attention deficit, memory impairment, as well as depression and anxiety disorders [19]. These symptoms are often independent of endocrine function, and can also be present in patients in a euthyroid state [16].

Thyroid function is most commonly evaluated by means of laboratory tests determining the levels of TSH and thyroid hormones. The thyroid

secretes two hormones regulating metabolism: thyroxine (T4) and triiodothyronine (T3). A decline in the level of thyroid hormones, through a negative feedback loop, stimulates the pituitary gland to increase the production of TSH [20, 21]. In patients with compensated hypothyroidism, which is asymptomatic, thyroid hormone levels are usually normal with slightly elevated TSH in blood serum. With progressive damage to the thyroid gland, the levels of thyroxine (T4) go down, while TSH goes up. In our study group, a strong majority of patients had thyroid hormone levels in the reference range. Values in the normal range for free thyroxine (FT4) were observed in 89.3% (183) of the participants, and for the thyroid stimulating hormone (TSH) – in 77.6% (159).

Numerous studies suggest that a somatic disease may impair the individual's functioning in daily life, which is naturally reflected in their mental state, manifesting itself as sadness, dejection or depressed mood [7]. With regard to Hashimoto's thyroiditis, mental health symptoms in the form of anxiety and depression disorders often precede the full-blown clinical manifestation of the disease [22]. Carta et al. reported an elevated risk for depressive disorders in patients with Hashimoto's disease independent of thyroid dysfunction [17]. Symptoms of depression in a group of patients with chronic thyroiditis, but normal levels of thyroid hormones were confirmed by the findings in Kirim et al. [23] and Ayhan et al. [24], who found these disorders also in euthyroid patients with diagnosed HT. Different findings were obtained by Engum et al. in a large population study [25], failing to confirm the relationship between autoimmune thyroiditis and depressive disorders. In the present study, more than half of the women suffering from Hashimoto's disease showed signs of depressive disorders, although symptoms of moderate and severe depression were found in a minority. Nevertheless, mild depression was confirmed in 40% of the studied women.

In turn, Itterman et al. found a positive association of untreated diagnosed hypothyroidism with depressive disorders and anxiety, as well as between severe symptoms of depression and untreated diagnosed hyperthyroidism [11]. It has even been suggested that patients with autoimmune thyroiditis are at risk for the development of depression and anxiety disorders [16]. The relationship between anxiety and hyperthyroidism/hypothyroidism is also confirmed by other authors [26, 27]. The research team led by Basińska obtained the surprising finding of a negative, statistically significant relationships between TSH and tension/anxiety. It would mean that higher TSH levels are associated with lower anxiety, linking the latter to hyperthyroidism, rather than hypothyroidism [7]. In the present study, anxiety disorders in the majority of women were of a moderate severity, but data analysis showed higher levels of state anxiety in women with higher TSH values.

The disorders of the hypothalamus-pituitary-thyroid axis present in Hashimoto's thyroiditis are without a doubt linked to affective disorders and depression. These disorders should be regarded as both mediators of the disease, and its consequences. The pathogenetic relationship between autoimmune thyroiditis and the development of neuro-psychiatric disorders is nevertheless still unclear and requires further research, seen as establishing the correct diagnosis is paramount in prescribing the right treatment and associated with improved prognosis.

CONCLUSIONS

1. Depressive symptoms co-occur with anxiety disorders in the group of women with Hashimoto's disease. The studied group of patients presented mild depressive symptoms and moderate anxiety disorders.
2. A higher level of state anxiety in the group of women with Hashimoto's disease is correlated with higher serum TSH.
3. Lower serum FT4 co-occurs with more severe symptoms of depression and anxiety.

Abbreviations
BDI-II:Beck Depression Inventory
HT: Hashimoto's thyroiditis
TSH: thyroid stimulating hormone
STAI: State-Trait Anxiety Inventory

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