Thyroid autoimmunity is associated with hypothyroid-like symptoms compared with nonautoimmune benign thyroid diseases using a thyroid-specific questionnaire

Tamer M. Elsherbiny

Endocrinology Unit, Internal Medicine Department, Alexandria Faculty of Medicine, Alexandria, Egypt

Correspondence to Tamer M. Elsherbiny, PhD, Endocrinology Unit, Internal Medicine Department, Alexandria Faculty of Medicine, Azarita, Alexandria, 21544, Egypt.
e-mail: tamer_elsherbiny@alexmed.edu.eg

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Background
Autoimmune hypothyroidism, also commonly known as Hashimoto thyroiditis (HT), is the most common cause of hypothyroidism in iodine-replete areas. Thyroid autoimmunity was shown to be associated with lower quality of life, higher symptom load, and poor physical and psychological well-being. The aim of this study is to evaluate the disease burden of HT using a thyroid-specific questionnaire, the thyroid patient reported outcomes (ThyPRO).
Patients and methods
The study included 194 patients, divided into two groups: group 1 included 124 patients with HT stable in euthyroidism 6 months before inclusion in the study, and group 2 included 70 patients with euthyroid benign thyroid disease other than HT. All patients completed a professionally translated, carefully revised version of the ThyPRO questionnaire into Arabic language. All patients had their thyroid stimulating hormone (TSH) measured at inclusion. Anti-thyroperoxidase and/or anti-thyroglobulin antibodies were recorded for each patient where available.
Results
There were no significant differences between the two studied groups regarding age, sex, and TSH. Both anti-thyroperoxidase and anti-thyroglobulin antibodies were significantly higher in HT group versus group 2. Group 1, HT group, showed significantly higher score in the hypothyroid symptom scale compared with group 2. No significant differences were found regarding the remaining symptom scales. Within hypothyroid symptom score scale, group 1 showed significantly higher scores in dry skin and swollen hands and feet items but not in cold sensitivity and itchy skin questions.
Conclusion
This study showed that thyroid autoimmunity, independent of thyroid function status, is associated with hypothyroid-like symptoms compared with benign thyroid disease other than HT. This may be caused by a direct or an indirect role of thyroid autoantibodies.

Keywords:
hypothyroid symptoms, ThyPRO questionnaire, thyroid autoimmunity

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Introduction

Hypothyroidism is the second most commonly prevalent endocrine disorder after diabetes mellitus. Prevalence of hypothyroidism is 4.6 and 4.9% in USA and Europe, respectively [1,2]. Autoimmune hypothyroidism, also commonly known as Hashimoto thyroiditis (HT), is the most common cause of hypothyroidism in iodine-replete areas, with an estimated prevalence of 5.13% of general population [2,3]. Epidemiologic evidence suggested an association between thyroid autoimmunity and anxiety and mood disorders [4]. Thereafter, several studies have shown that thyroid autoimmunity, apart from hypothyroidism, was shown to be associated with lower quality of life (QoL), higher symptom load, poor physical and psychological well-being, and poor attention performance. Nonspecific tools were used to evaluate these patients like SF-36 questionnaire, Symptom Checklist-90-Revised, Beck Depression Inventory, Beck Anxiety Inventory tests, and the D2 attention test [5–9]. Thyroid patient reported outcomes (ThyPRO) is a thyroid-specific comprehensive questionnaire that measures the effect of benign thyroid disease on health-related QoL. A recent meta-analysis recommended the assessment of health-related QoL in patients with benign thyroid diseases using ThyPRO [10,11].

The aim of this study is to evaluate the disease burden of HT – independent of thyroid function status –

versus other benign thyroid diseases using a thyroid-specific health-related QoL measure, the ThyPRO.

Patients and methods

The study was conducted on 194 patients with benign thyroid disease. They were divided into two groups: group 1 included 124 patients with HT, and group 2 included 70 patients with benign thyroid disease other than HT. All patients were either euthyroid or rendered euthyroid by treatment. They were stable in euthyroidism for at least 6 months before inclusion in the study.

Exclusion criteria included hypothyroidism, hyperthyroidism, thyroid carcinoma, past history or current treatment for psychiatric illness (depression or anxiety disorders), diabetes, chronic liver, or kidney diseases.

A diagnosis of HT was based on one of the following criteria: positive thyroid autoantibodies [anti-thyroperoxidase (anti-TPO) antibodies and/or anti-thyroglobulin (anti-TG) antibodies], positive thyroid sonography for autoimmune thyroid disease (diffuse hypoechogenicity, heterogenicity, and pseudonodules), or both [12].

Alexandria Faculty of Medicine Ethical committee approved the protocol of the study, and all study participants provided a written informed consent after being explained the nature and aim of the study.

Methods

All patients completed a professionally translated, carefully revised version of the ThyPRO questionnaire into Arabic language. ThyPRO consists of 84 questions, grouped in 13 scales, namely, goiter symptoms, hyperthyroid symptoms, eye symptoms, hypothyroid symptoms, tiredness, cognition, anxiety, depressivity, emotional susceptibility, impaired social life, impaired daily life, impaired sex life, cosmetic complaints, and one single question which measures general health-related QoL. Sex life domain was deliberately omitted from the questionnaire, because asking about sex life is not accepted culturally by most Egyptian patients. Each question was scored on a five-point scoring system from 0=not at all to 4=very much, with a 4-week reference period. The multi-question scales were derived by averaging question scores within a scale and linearly transforming them to a 0–100 scale with 0 being the best and 100 being the worst possible score [13].

All patients had their thyroid stimulating hormone (TSH) measured at inclusion to ensure euthyroidism. Anti-TPO antibodies and/or anti-TG antibodies were recorded for each patient where available.

Data were analyzed using IBM SPSS software package version 20.0 (IBM Corp., Armonk, New York, USA). Significance of the obtained results was judged at the 5% level.

Results

Group 1 included 124 patients with HT: 22 were euthyroid, and 102 were hypothyroid. They were rendered euthyroid by l-thyroxine treatment. All of them were stable in euthyroidism 6 months before inclusion in the study. Group 2 included 70 patients with benign thyroid disease other than HT. Their diagnoses were 24 patients with postsurgical hypothyroidism (22 total and two hemithyroidectomies), 24 patients with nodular thyroid disease (uninodular or multinodular disease), 11 patients with autoimmune disease other than HT (Graves' disease and post-partum thyroiditis), and 11 patients with other diagnosis (de Quervain's thyroiditis, congenital, and amiodarone-induced hypothyroidism). All of them were stable in euthyroidism 6 months before inclusion in the study.

Both study groups were matched for age. Mean age was 37.7 years for group 1, and 38.3 years for group 2. Most patients of both groups were female: 94.4% of group 1 and 87.1% of group 2. Mean TSH for both groups was similar: 1.5 mIU/l for group 1 and 1.6 mIU/l for group 2 (Table 1).

As expected, both anti-TPO antibodies and anti-TG antibodies were significantly higher in HT group versus group 2 (Table 1).

Regarding the ThyPRO questionnaire, group 1, HT group, showed significantly higher score in the hypothyroid symptoms scale compared with group 2. No significant differences were found regarding the other 11 symptom scales and the question assessing general health-related QoL between the two studied groups (Table 2).

When individual items of the hypothyroid symptoms score scale were analyzed, group 1, HT group, showed significantly higher score in dry skin and swollen hands

Table 1 Comparison between the two studied groups according to age, sex, TSH at inclusion, and thyroid autoantibodies

	Total (n=194)	Diagnosis		Test of significance	P
		Hashimoto (n=124)	Other (n=70)		
Age (years)					
Mean±SD	37.9±12.8	37.7±12.3	38.3±13.8	t=0.323	0.747
Median (minimum–maximum)	37 (14–70)	37.5 (17–65)	36 (14–70)		
Sex					
Male	16 (8.2)	7 (5.6)	9 (12.9)	χ^2=3.075	0.079
Female	178 (91.8)	117 (94.4)	61 (87.1)		
Mean TSH					
Mean±SD	1.6±0.8	1.6±0.8	1.5±0.8	U=4164.50	0.640
Median (minimum–maximum)	1.5 (0.2–3.8)	1.5 (0.3–3.8)	1.6 (0.2–3.8)		
Anti-TG					
Mean±SD	367.2±645.2	408.2±688.1	180.4±350.4	U=354.0*	0.001*
Median (minimum–maximum)	171.5 (12–4000)	186 (17.6–4000)	23 (12–1370)		
Anti-TPO					
Mean±SD	258.6±281.7	299.2±285.7	76.6±173.7	U=440.50*	<0.001*
Median (minimum–maximum)	149.5 (1–1300)	204 (1–1300)	17 (5–600)		

TSH, thyroid stimulating hormone; χ^2, P: χ^2 and P values for χ^2-test for comparing between the two groups. t, P: t and P values for Student t-test for comparing between the two groups. U, P: U and P values for Mann–Whitney test for comparing between the two groups. *$P \leq 0.05$, statistically significant.

and feet items but not in cold sensitivity and itchy skin questions (Table 3).

Group 1, HT group, was subclassified into treated, 102 patients, and nontreated, 22 patients. When the subgroups were compared with group 2, nontreated HT showed significantly higher score in the hypothyroid symptoms scale compared with group 2; however, treated HT showed no significant differences in the hypothyroid symptoms scale compared with group 2.

No correlation was found between hypothyroid symptom scale score in ThyPRO questionnaire and TSH, anti-TPO, or anti-TG antibodies in HT group.

Discussion

The main finding of this study is that patients with HT experience hypothyroid-like symptoms, namely, dry skin and swollen hands and feet despite being euthyroid using levothyroxine for 6 months compared with patients with euthyroid non-Hashimoto benign thyroid disease. The evaluation of thyroid-related symptoms in both study groups was done using the ThyPRO questionnaire, a thyroid-specific tool to evaluate thyroid-related patient-reported outcomes.

The results of this study suggest that thyroid autoimmunity may be the causative of these hypothyroid-like symptoms, that is, the dry skin and swollen hands and feet, because they only occurred in patients with HT but not in non-Hashimoto benign thyroid disease, despite being matched for age, sex, and euthyroidism.

Ott *et al.* [5] were the first to report an association between thyroid autoimmunity and symptom burden in HT. They compared 47 patients with HT with 379 non-HT benign thyroid disease using SF-36 and a 13-hypothyroid symptom list. They found that patients with HT significantly experienced more chronic fatigue, dry hair, easy fatigue, dysphagia, chronic irritability, and nervousness. They also found that thyroperoxidase antibodies correlated with symptoms score and a lower QoL assessed by SF-36. Mean TSH of patients with HT in their study was 1.6 mIU/ml, very similar to this study (1.7 mIU/ml). The main advantage in this study is the use of a thyroid-specific questionnaire (ThyPRO), rather than a generic one (SF-36) to evaluate symptom burden.

Similar results were reported by Mussig *et al.* [8] and Bektas Uysal *et al.* [6]. They also used generic tools to evaluate symptoms burden, SCL-90-R and SF-36, respectively. They included a smaller number of euthyroid patients with HT compared with this study, that is, 64 and 84 patients, respectively. Mussig *et al.* [8] reported that thyroperoxidase antibodies correlated with psychological distress, intensity of symptoms, and number of reported symptoms; they also predicted poor psychological well-being. Bektas Uysal *et al.* [6] reported that higher thyroperoxidase and thyroglobulin antibodies correlated with lower QoL scores and lower individual domain scores.

Table 2 Comparison between the two studied groups according to mean % score of different domains of the ThyPRO questionnaire

Mean % score	Total (*n*=194)	Diagnosis		*U*	*P*
		Hashimoto (*n*=124)	Other (*n*=70)		
Goiter symptoms					
Mean±SD	12.2±14	11±11.9	14.4±16.9	3795.0	0.144
Median (minimum–maximum)	7.5 (0–100)	6.8 (0–50)	10.2 (0–100)		
Hyperthyroid symptoms					
Mean±SD	22.8±17.8	23.4±17.4	21.7±18.6	3955.0	0.304
Median (minimum–maximum)	18.8 (0–95.8)	21.7 (0–95.8)	15.6 (0–81.3)		
Eye symptoms					
Mean±SD	16.9±16.6	16.8±16.2	17±17.4	4225.5	0.759
Median (minimum–maximum)	12.5 (0–81.3)	12.5 (0–81.3)	13.4 (0–75)		
Hypothyroid symptom					
Mean±SD	21.2±20.4	23.2±20.8	17.6±19.4	3579.0*	0.040*
Median (minimum–maximum)	12.5 (0–75)	18.8 (0–75)	12.5 (0–75)		
Tiredness					
Mean±SD	40.6±19.4	41.6±18.2	38.8±21.4	3972.0	0.326
Median (minimum–maximum)	39.3 (0–100)	39.3 (3.6–100)	35.7 (0–92.9)		
Cognition					
Mean±SD	27.4±24.2	27.7±24.1	26.7±24.4	4171.0	0.652
Median (minimum–maximum)	25 (0–100)	25 (0–100)	25 (0–100)		
Anxiety					
Mean±SD	42±26.2	41.3±26.5	43.2±25.6	4110.0	0.540
Median (minimum–maximum)	37.5 (0–100)	39.6 (0–100)	35.4 (0–100)		
Depressivity					
Mean±SD	42.1±21	40.7±20.3	44.6±22.1	4010.50	0.380
Median (minimum–maximum)	39.3 (0–100)	39.3 (0–100)	38.4 (14.3–89.3)		
Emotional susceptibility					
Mean±SD	41.3±18.1	41.6±17.9	40.8±18.7	4225.50	0.760
Median (minimum–maximum)	41.7 (0–94.4)	41.7 (4.2–94.4)	39.8 (0–77.8)		
Impaired social life					
Mean±SD	24.2±23.8	23.2±23.8	26.1±23.9	3974.50	0.410
Median (minimum–maximum)	18.8 (0–100)	12.5 (0–100)	18.8 (0–93.8)		
Impaired daily life					
Mean±SD	15.8±21.3	16±22.2	15.4±19.6	4130.0	0.681
Median (minimum–maximum)	4.2 (0–100)	4.2 (0–100)	8.3 (0–75)		
Cosmetic concern					
Mean±SD	16±22.9	16.8±24.7	14.5±19.2	4144.50	0.781
Median (minimum–maximum)	4.2 (0–100)	4.2 (0–100)	8.3 (0–83.3)		
Has your thyroid disease had a negative effect on your quality of life?					
Mean±SD	18.8±25.4	17.5±25	21.3±26	3783.50	0.228
Median (minimum–maximum)	0 (0–100)	0 (0–100)	25 (0–100)		

THyPRO, thyroid patient reported outcomes; *U*, *P*: *U* and *P* values for Mann–Whitney test for comparing between the two groups.
*$P \leq 0.05$, statistically significant.

Recently, Baric *et al.* [14] evaluated 290 untreated patients with HT using a 16-hypothyroid symptom list and found that thyroglobulin antibodies but not thyroperoxidase antibodies positively correlated with number of reported symptoms, and were associated with symptoms of fragile hair, face edema, eyes edema, and harsh voice. Median TSH in this study was 3.7 mIU/ml, 17% of the patients had overt HT, whereas remaining of the patients were either euthyroid or subclinically hypothyroid. In agreement with this study, HT-related symptoms were skin related; however, unlike this study, a significant percentage of their patients were overtly or subclinically hypothyroid. They also used a symptom list rather than a validated thyroid-specific questionnaire like ThyPRO.

Thyroid autoimmunity is not only associated with symptom burden, it was reported to be a possible causative factor of fibromyalgia. In this study, HT was found to be associated with visual analog scale pain and fatigue. Euthyroid patients with HT assessed by Beck Depression and Anxiety inventories were found to have a higher risk of current depressive or

Table 3 Comparison between the two studied groups according to items of hypothyroid symptom score of the ThyPRO questionnaire

Hypothyroid score	Total (*n*=194)	Diagnosis		*U*	*P*
		Hashimoto (*n*=124)	Other (*n*=70)		
Sensitive to cold					
Mean±SD	0.9±1.2	1±1.2	0.8±1.1	3509.5	0.225
Median (minimum–maximum)	0 (0–4)	0.5 (0–4)	0 (0–4)		
Swollen hands or feet					
Mean±SD	0.6±1	0.7±1	0.3±0.8	3442.5*	0.007*
Median (minimum–maximum)	0 (0–4)	0 (0–4)	0 (0–3)		
Dry skin					
Mean±SD	1±1.2	1.2±1.2	0.8±1.2	3358.5*	0.011*
Median (minimum–maximum)	1 (0–4)	1 (0–4)	0 (0–4)		
Itchy skin					
Mean±SD	0.8±1.1	0.9±1.2	0.8±1	4256.5	0.886
Median (minimum–maximum)	0 (0–4)	0 (0–4)	0 (0–4)		

THyPRO, thyroid patient reported outcomes; *U*, *P*, *U* and *P* values for Mann–Whitney test for comparing between the two groups.
*$P \leq 0.05$, statistically significant.

anxiety disorders, weakness of attention using D2 test, and lower mental health scores using SF-36, with a negative correlation between mental health scores and thyroperoxidase antibodies. A recent meta-analysis concluded that the odds ratio of depression and anxiety in HT are 3.5 and 2.3, respectively [7,9,15–17].

Possible mechanisms to explain the association between thyroid autoimmunity and physical and psychological well-being despite euthyroidism would fall into one of four categories: thyroid autoantibodies, selenium deficiency, thyroid hormone fluctuations, or disease self-awareness.

Thyroglobulin receptors were found to be expressed in a number of nonthyroidal tissues including brain and skin. The exact role of these receptors in such tissues is not known. Thyroglobulin autoantibodies may interfere with this function. This may explain the association between thyroid autoimmunity and urticaria and vitiligo. It may also explain the skin related hypothyroid-like symptoms reported in this study and other cited reports [14].

Both thyroperoxidase and thyroglobulin antibodies were found in the cerebro spinal fluid (CSF) of patients with Hashimoto encephalopathy, a steroid responsive central nervous system (CNS) disease with neuropsychiatric manifestations associated with thyroid autoimmunity, and thyroperoxidase antibodies were found to bind human brain astrocytes, which may suggest a direct role in the pathogenesis of neuropsychiatric manifestations of thyroid autoimmunity through induction of vasculitis, cerebral hypoperfusion, or decreased gray matter density [9,18,19].

However, thyroperoxidase and thyroglobulin antibodies may not have a direct role in HT-associated symptom burden; they may only represent a marker of polyclonal autoimmune response against multiple organ-specific autoantigens that mediate the perceived symptom burden. Autoantibodies to muscle proteins might link muscular pains to thyroid autoimmunity. Autoantibodies to CNS linked to disrupted myelinogenesis and gangliosides autoantibodies linked to disrupted axonal regeneration were detected in euthyroid patients with HT. Immune activation-associated thyroid autoimmunity is associated with monocyte/T-lymphocytes cytokines profile (Monocyte Chemoattractant Protein-1 (MCP-1), Tumour Necrosis Factor alpha (TNF-α), Interferon gamma (IFN-γ)) that have a negative effect on formation, release, and reuptake of serotonin, dopamine, and glutamate neurotransmitters [6,14,15,18,20].

Lack of a significant correlation between anti-TPO or anti-TG antibodies and hypothyroid symptom score in this study is in favor of an indirect rather than a direct role of thyroid autoantibodies in HT-associated symptom burden.

Selenium deficiency, a known risk factor for the development of thyroid autoimmunity, was shown to affect behavior, mood, and cognitive functions; thus, it may contribute to mental health symptom burden in euthyroid HT [5].Fluctuations in the thyroid function with periods of transient subclinical hypothyroidism is a well-known phenomenon in HT; thus, hypothyroid-like symptoms may be caused by temporary hypothyroidism undetectable by widely spaced biochemical follow-up regimen [5,6].

Lastly, awareness of having HT, especially with the widely available, easily accessible patient information about the disease on the internet, may account for the perceived symptom load; therefore, we tried to control for the effect of disease awareness in this study by choosing our control group as benign thyroid disease with a similar disease awareness stress [6,7].

The strengths of this study include the large number of patients with HT evaluated compared with many other cited studies including less than a hundred patients; the use of patients with euthyroid benign thyroid disease as a control group to control for the burden of having a chronic illness on the results; and finally, the use of a thyroid-specific questionnaire, the ThyPRO, which is recommended for use in patients with benign thyroid diseases.

Conclusion

This study showed that thyroid autoimmunity is associated with hypothyroid-like symptoms compared with benign thyroid disease other than HT. This may be caused by a direct or an indirect role of thyroid autoantibodies.

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Conflicts of interest

There are no conflicts of interest.

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