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ORIGINAL ARTICLE

Autoimmunity affects health-related quality of life in patients with Hashimoto's thyroiditis

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Abstract Hashimoto's thyroiditis (HT) is the most common endocrine disorder leading to hypothyroidism. HT is characterized by the presence of elevated circulating antibodies, especially anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg). In our study, we aimed to reveal the effects of autoimmunity on health-related quality of life of euthyroid HT patients. Patients who were admitted to the Adnan Menderes University Outpatient Clinic were enrolled. The medical records of the patients were surveyed and their demographical data were collected. By using communication data, the patients were invited to our clinic, to inform them about our study and to fill out the health-related quality of life questionnaire. A total of 84 euthyroid HT patients older than 18 years who completed the short form-36 questionnaire, were enrolled. As all patients were euthyroid, there was a significant negative correlation between each domain score and the antibody levels, individually. Patients who had higher anti-TPO and anti-Tg levels had significantly lower quality of life domain scores ($p < 0.001$). There was statistically no significant correlation between the antibody levels and thyroid function tests ($p > 0.05$). Additionally, all dimension scores were significantly higher both in the anti-Tg and anti-TPO negative groups, indicating a better quality of life than that in the antibody positive groups. Our study revealed that higher thyroid antibody levels were negatively correlated with life quality scores. Thus, patients who had higher anti-TPO and anti-Tg levels had significantly lower quality of life domain scores. We believe that apart from hypothyroidism, a high antibody level was one of the contributing factors for the development of HT-associated symptoms, leading to a lower quality of life. Other probable contributing factors such as selenium deficiency, thyroid hormone fluctuation, and disease awareness should keep in mind.

Conflicts of interest: All authors declare no conflicts of interests.

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Introduction

Hashimoto thyroiditis (HT) is the most common endocrine disorder leading to hypothyroidism. The disease is considered to be the most common autoimmune disease. HT is characterized by the presence of elevated circulating antibodies to thyroid antigens, especially the anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) antibodies [1]. The disease is diagnosed by clinical properties, presence of serum antibodies, and the sonographic appearance of thyroid. Anti-TPO is considered to be the best serological marker for the diagnosis of HT and is found positive in nearly 95% of the patients. It has been shown that anti-TPO titers are positively correlated with the number of thyroid-infiltrating lymphocytes and with the sonographic hypoechogenicity degree of the thyroid [2]. Anti-Tg antibodies are positive in nearly 60–70% of HT patients and are found to be positive in a higher proportion of healthy people. They are less specific and sensitive for HT when compared with anti-TPO antibodies [3]. As the two antibodies are assessed together for the diagnosis in daily practice, they correlate poorly. In HT, anti-TPO levels are expected to be at higher titers than anti-Tg levels [1].

The influence of a chronic disease on the everyday life of a patient is very important. Health-related quality of life (HRQoL) is 'a general concept that implies an evaluation of the impact of all aspects of life on the general well-being' [4]. In other words, it is the subjective assessment of how a medical situation affects the daily physical, emotional, social functioning, and well-being of a person [5]. When treating a chronic disorder such as HT, the HRQoL of the patient may be damaged because of different contributing factors. Concurrently with medical examinations, measuring HRQoL in daily clinical practice may give important information about patients with particular difficulties, which may need support, and about the effects of the treatment modalities or the patients' emotional moods. In the last decade especially, HRQoL has been one of the main targets of chronic disease treatment.

The importance of HRQoL has also increasingly been acknowledged for thyroid disorders by some recent studies [6–9]. To date, hypothyroidism is thought to be the main factor for the increased symptom load and decreased quality of life. However, studies have revealed that thyroid disorders affect HRQoL, independently of the thyroid function status. Even in euthyroid patients HRQoL was also found to be decreased [7]. From this point of view, we aimed to reveal other contributing factors of decreased quality of life.

It is known that thyroid dysfunctions and mood disorders, especially depression, often exist together [10]. Autoimmunity in the thyroid gland, mostly anti-TPO, was found to be closely linked with decreased quality of life and a depressed mood [7,11]. However, there are conflicting studies suggesting that there is no association [12].

In our present study, we aimed to reveal the effects of autoimmunity on HRQoL of euthyroid HT patients. Furthermore, to the best of our knowledge, this is the first study assessing the impact of two antibodies, anti-TPO and anti-Tg together on HRQoL.

Materials and methods

Study design

Patients with HT diagnosis who were admitted to Adnan Menderes University Outpatient Clinic between December 2013 and January 2016 were enrolled in our study. The HT diagnosis was based on histological validation or clinical properties, presence of serum antibodies, and sonographic findings. Among all selected participants, there were 13 patients with negative antibody but diagnosed with histological examination. The medical records of patients were surveyed and the demographic data collected. Patients who had thyroid function test results in the last 6 months and thyroid antibody test results were selected. Normal ranges in our laboratory for thyroid stimulating hormone (TSH) and free thyroxine (fT4) were 0.35–4.94 IU/mL and 0.70–1.48 ng/dL, respectively. Patients who had hyperthyroidism (decreased TSH and increased fT4 levels) or hypothyroidism (increased TSH and decreased fT4 levels) were excluded. Patients with subclinical thyroid dysfunctions were not included; only euthyroid patients were included. Clinical variables including age, associating chronic diseases, and treatment options were completed during the survey. By using the communication data, patients were invited to our clinics to be informed about our study and to fill out the HRQoL questionnaire. Written informed consent of patients who agreed to participate in the study was taken. Participants older than 18 years who completed the SF-36 questionnaire were enrolled in the study. Patients having psychiatric disorders, dementia, pregnancy, inflammatory diseases, acute infections and malignancy were excluded from the study. Additionally, patients having mental or social retardation, who were unable to complete the questionnaire, were also excluded. This study was approved by the Ethics Committee of the Adnan Menderes University Faculty of Medicine, Aydin, Turkey.

HRQoL measurement

SF-36 is a self-completed questionnaire measuring eight aspects of health status: (1) physical functioning (PF)—the extent of health limiting physical activity; (2) physical role playing (RP)—the extent of physical health interfering or limiting the usual role activities; (3) emotional role playing (RE)—the extent of emotional problems interfering or limiting the usual daily role activities; (4) social functioning (SF)—the extent of physical health or emotional problems interfering with the normal social activities; (5) bodily pain (BP)—the intensity of pain and effects on normal activities; (6) mental health (MH)—includes depression and anxiety; (7) vitality (VT)—including feeling full of pep versus tired and worn-out; and (8) general health (GH)—personal evaluation of health. SF-36 measures these eight health dimensions with 36 items: PF with 10 items; RP and VT each with four items; RE with three items; SF and BP each with two items; and GH and MH each with five items. There is a further unscaled single item asking respondents about health change over the past year. For each dimension, the

item scores are coded, summed, and transformed on to a scale from 0 (worst possible health state measured by the questionnaire) to 100 (the best possible health state) [13]. The scores represent the percentage of the total possible score achieved. Following this, the items in the same scale are averaged together to create the eight dimension scores. Physical composite scores (PCS) and mental composite scores (MCS) were calculated for the SF-36 as described by Ware et al. [13,14]. PCS defines the general physical health status and MCS defines the general mental health status. The SF-36 questionnaire is widely used in chronically ill patients and has significant correlations with other HRQoL measures [14]. Moreover, adequate internal consistency reliabilities (0.81–0.88) support its use [15]. The reliability of the Turkish version of SF-36 has been proved by Koçyiğit et al. [16].

Statistical analysis

All data were analyzed by using the PASW Statistics version 18 (SPSS Inc., Chicago, IL, USA) software package. The Kolmogorov–Smirnov test was used to assess the normality of the numeric variables. Descriptive analyses were presented using the mean ± standard deviation or median (25^{th} percentile to 75^{th} percentile values) for continuous variables and percentage values were given for categorical variables. Student *t* and Mann–Whitney *U* tests were used to compare the parametric continuous variables in the independent groups and Chi-square tests were used for the comparison of categorical variables. The Spearman's coefficient was used to measure correlations among the quality of life scores, the antibody levels, and thyroid function test levels. Additionally, patients were stratified into groups according to their serum antibody levels. Patients with positive anti-TPO levels and negative anti-TPO levels were assessed according to their HRQoL domain scores using the Mann–Whitney *U* test. Similar assessments were performed according to the anti-Tg levels, too. An overall 0.05 type-1 error level was used to infer the statistical significance.

Results

A total of 84 patients, 94% women and 6% men were enrolled in our study. The mean age of the group was 41.82 ± 12.16 years. The patient characteristics are presented in Table 1. Eighteen patients had additional comorbidities except psychiatric disorders, dementia, pregnancy, inflammatory diseases, acute infections, malignancy, and mental retardation. All patients had normal fT4 and TSH levels within normal ranges. Fifty-two patients (62% of the study population) were under thyroid hormone supplementation. All patients with and without thyroid hormone supplementation were euthyroid.

Overall, the HRQoL domain scores of the study population, expressed as median (25^{th}–75^{th} percentile) values, were as follows: PF 80.00 (56.25–90.00); RP 50.00 (0.00–75.00); BP 62.00 (41.00–74.00); GH 43.50 (30.00–65.00); VT 32.50 (20.00–63.75); SF 50.00(37.50–75.00); RE 33.30 (0.00–66.70); MH 52.00 (33.00–68.00); PCS 44.40 (36.57–51.22); and MCS 34.55 (27.85–43.75).

Table 1 Demographic and clinical characteristics of patients.

Variable	Value
Sex (female), *n* (%)	79 (94)
Patients with thyroid hormone supplementation, *n* (%)	52 (62)
Patients with comorbidity, *n* (%)	18 (21)
Age (y), mean ± standard deviation	41.82 ± 12.16
TSH (μU/mL), median (25^{th}–75^{th} percentile)	1.89 (0.96–3.22)
fT4 (ng/dL), median (25^{th}–75^{th} percentile)	1.10 (0.99–1.19)
Anti-TPO (IU/mL), median (25^{th}–75^{th} percentile)	287.19 (22.72–762.20)
Anti-Tg (IU/mL), median (25^{th}–75^{th} percentile)	24.82 (3.38–160.07)

Anti-Tg = anti-thyroglobulin antibody; Anti-TPO = anti-thyroperoxidase antibody; fT4 = free thyroxine; TSH = thyroid stimulating hormone.

As shown in Table 2, there was a significant negative correlation between each SF-36 domain score and antibody level, individually. Patients who had higher anti-TPO and anti-Tg levels had a significantly lower quality of life domain scores ($p < 0.001$). There was no statistically significant correlation between the antibody levels and thyroid function tests ($p > 0.05$). Additionally, there was no significant correlation between the TSH or fT4 levels and the HRQoL domain scores ($p > 0.05$).

Patients were stratified according to their antibody levels. When anti-TPO positive patients were compared with those with negative anti-TPO, no difference was found in the prevalence in female patients [62 (94%) vs. 17 (94%), $p > 0.05$] age and thyroid hormone supplementation [41 (62%) vs. 11 (61%), $p > 0.05$]. There was also no significant difference in TSH [1.89 (0.98–3.32) vs.1.87 (0.93–2.96), $p > 0.05$] and fT4 [1.09 (0.99–1.199 vs 1.14 (0.96–1.20), $p > 0.05$] levels between anti-TPO positive and negative groups. Similarly, there were no significant differences between anti-Tg positive and negative groups in terms of sex [56 (93%) vs. 23 (96%), $p > 0.05$], age, thyroid hormone supplementation [37 (62%) vs. 15 (62%), $p > 0.05$], TSH [1.89 (1.00–3.40) vs. 1.88 (0.92–2.75), $p > 0.05$] and fT4 [1.09 (0.99–1.19) vs. 1.10 (0.98–1.23), $p > 0.05$] levels. As mentioned above, the groups were similar in terms of some important probable confounding factors such as age, sex, thyroid hormone supplementation and thyroid hormone levels. All dimension scores were significantly higher both in anti-Tg and anti-TPO negative groups, indicating a better quality of life than in the antibody positive groups ($p < 0.001$). When these groups were stratified by adjusting the comorbidities as a confounding factor; there was also a significant difference between both anti-TPO and anti-Tg antibody positive and negative groups ($p < 0.001$). SF-36 domain scores in antibody positive and negative groups, by adjusting comorbidities, are as presented in Tables 3 and 4.

Table 2 Relationship between health related quality of life scores and antibody levels by Spearman's correlation coefficient.

	PF	RP	BP	GH	VT	SF	RE	MH	PCS	MCS
Anti-TPO	−0.73*	−0.76*	−0.71*	−0.69*	−0.79*	−0.55*	−0.62*	−0.68*	−0.76*	−0.64*
Anti-Tg	−0.57*	−0.65*	−0.54*	−0.65*	−0.63*	−0.51*	−0.49*	−0.56*	−0.62*	−0.56*

The Spearman's coefficient was used to measure correlations. $p < 0.05$ was defined as statistically significant. * Correlation is significant at the 0.01 level (2-tailed).
Anti-Tg = anti-thyroglobulin antibody; Anti-TPO = anti-thyroperoxidase antibody.

Discussion

It is well-known that thyroid dysfunction affects the mental and physical dimensions of personal health and decreases the HRQoL of patients [17]. Most of the studies point out the presence of hypothyroidism and the related reduction in the HRQoL of patients. However, euthyroid patients still suffer from a general indisposition with various presentations. Our study clearly reveals that HT impacts the perceived health status independently from the thyroid function state. In the study by Demiral et al. [18], the population norms of the SF-36 health survey in Turkey has been determined. According to this Turkish norm-based SF-36, the mean ± standard deviation (median) dimension scores are: PF 83.8 ± 20.0 (100); RP 86.3 ± 24.9 (100); BP 82.9 ± 18.9 (100); GH 71.6 ± 16.1 (72); VT 64.5 ± 12.9 (70); SF 91.0 ± 12.9 (100); RE 90.1 ± 19.4 (100); MH 71.0 ± 11.0 (76); PCS 47.9 ± 8.9 (54); and MCS 47.7 ± 9.4 (52). When compared with the Turkish general population norms, all domains are evidently lower in our study group, indicating a poorer quality of life in HT patients. This poor HRQoL status in euthyroid HT patients may have a few explanations. The contributing factors may be disease awareness, subclinical hypothyroidism, fluctuating thyroid hormone levels, and antibody load, individually.

In some other chronic diseases such as hepatitis C, only the awareness of the disease may lead to poorer HRQoL in patients [19]. Therefore, solely the HT disease awareness may be one of the contributing factors of poor HRQoL in our patients.

The most relevant result of our study was the strong association of both the higher anti-TPO and anti-Tg levels with a lower HRQoL. In a few previous studies, a negative correlation between HRQoL and anti-TPO has been observed [7,20]. To the best of our knowledge this is the first study demonstrating the negative correlation between anti-Tg and HRQoL, entirely. Some researchers have thought that if the antibody load itself is the main impacting factor on the HRQoL, substantial reduction of the antibody may help to improve the quality of life. It is known

Table 3 Health related quality of life (HRQoL) domain scores in comparison with anti-thyroperoxidase antibody (Anti-TPO) levels by adjusting comorbidities.

Comorbidity	HRQoL domain	Anti−TPO (−) $n = 18$	Anti−TPO (+) $n = 66$	p*
Yes	PF	92.50 (86.25−98.75)	67.50 (27.50−86.25)	0.01
	RP	100.00 (100.0−100.00)	25.00 (0.00−56.25)	< 0.001
	BP	79.00 (74.00−84.00)	41.00 (22.00−74.00)	< 0.001
	GH	77.00 (64.50−85.75)	42.00 (30.00−52.00)	< 0.001
	VT	82.50 (72.50−85.00)	27.50 (20.00−42.50)	< 0.001
	SF	93.75 (78.12−100.00)	56.25 (34.37−65.62)	< 0.001
	RE	100.00 (100.00−100.00)	0.00 (0.00−33.30)	< 0.001
	MH	80.00 (73.00−84.00)	44.00 (32.00−56.00)	< 0.001
	PCS	53.15 (50.15−55.70)	39.95 (28.05−47.00)	0.01
	MCS	54.30 (52.15−58.25)	32.90 (27.95−38.07)	< 0.001
No	PF	95.00 (90.00−100.00)	70.00 (55.00−80.00)	< 0.001
	RP	100.00 (75.00−100.00)	25.00 (0.00−50.00)	< 0.001
	BP	84.00 (74.00−100.00)	57.00 (41.00−74.00)	< 0.001
	GH	67.00 (57.00−73.25)	40.00 (25.50−50.00)	< 0.001
	VT	72.50 (60.00−81.25)	25.00 (15.00−40.00)	< 0.001
	SF	75.00 (59.37−100.00)	50.00 (37.50−62.50)	< 0.001
	RE	83.35 (58.35−100.0)	33.30 (0.00−33.30)	< 0.001
	MH	76.00 (63.00−80.00)	46.00 (28.00−60.00)	< 0.001
	PCS	54.05 (50.80−57.85)	40.95 (35.20−47.07)	< 0.001
	MCS	47.00 (43.20−52.10)	32.25 (24.40−39.37)	< 0.001

*Mann−Whitney U test, $p < 0.05$ was statistically significant. Data are reported as median (25^{th}−75^{th} percentile).
BP = bodily pain; GH = general health; MCS = mental composite scores; MH = mental health; PCS = physical composite scores; PF = physical functioning; RE = role emotional; RP = role playing; SF = social functioning; VT = vitality.

Table 4 Health-related quality of life (HRQoL) domain scores in comparison with anti-thyroglobulin antibody (Anti-Tg) levels by adjusting comorbidities.

Comorbidity	HRQoL Domain	Anti-Tg (−) $n = 24$	Anti-Tg (+) $n = 60$	p*
Yes	PF	90.00 (80.00—95.00)	55.00 (25.00—70.00)	0.01
	RP	75.00 (50.00—100.00)	0.00 (0.00—25.00)	< 0.001
	BP	74.00 (57.50—84.00)	41.00 (22.00—51.50)	0.01
	GH	62.00 (44.50—77.00)	40.00 (30.00—48.50)	0.03
	VT	70.00 (37.50— 82.50)	20.00 (17.50—35.00)	< 0.001
	SF	75.00 (62.50—93.75)	50.00 (25.00—65.50)	< 0.001
	RE	100.00 (33.30—100.00)	0.00 (0.00—16.65)	< 0.001
	MH	72.00 (44.00—80.00)	40.00 (30.00—52.00)	0.02
	PCS	50.90 (45.20—53.65)	39.60 (27.80—41.90)	< 0.001
	MCS	47.30 (34.95—54.30)	29.70 (25.85—36.15)	< 0.001
No	PF	95.00 (90.00—100.00)	70.00 (55.00—80.00)	< 0.001
	RP	100.00 (100.00—100.00)	25.00 (0.00—50.00)	< 0.001
	BP	100.00 (74.00—100.00)	52.00 (41.00—74.00)	< 0.001
	GH	72.00 (67.00—77.00)	40.00 (25.00—47.00)	< 0.001
	VT	75.00 (65.00—80.00)	25.00 (15.00—40.00)	< 0.001
	SF	75.00 (62.50—87.50)	50.00 (37.50—62.50)	< 0.001
	RE	66.70 (33.30—100.0)	33.30 (0.00—33.30)	< 0.001
	MH	76.00 (64.00—80.00)	48.00 (28.00—60.00)	< 0.001
	PCS	57.70 (54.00—59.90)	40.70 (35.00—46.20)	< 0.001
	MCS	47.40 (42.90—51.10)	32.20 (25.60—40.00)	< 0.001

*Mann—Whitney U test, $p < 0.05$ was statistically significant. Data are reported as median (25^{th}—75^{th} percentile).
BP = bodily pain; GH = general health; MCS = mental composite scores; MH = mental health; PCS = physical composite scores; PF = physical functioning; RE = role emotional; RP = role playing; SF = social functioning; VT = vitality.

that total or near total removal of the thyroid gland by surgery leads to the reduction in antibody loads [21]. However, it was revealed by Promberger et al. [8] that thyroidectomy is not a convenient option for increasing HRQoL of HT patients, who have high anti-TPO antibody levels. Additionally, after surgery, the lifelong overt hypothyroidism and impaired immunity status should be considered, as the quality of life may be further affected by these factors.

As an autoimmune disease, numerous organ-specific and nonorgan-specific diseases are known to associate with HT [22]. These associating autoimmune diseases are thought to be the contributing factors for the lower HRQoL scores in HT. In the serum of patients with autoimmune thyroid disease there is a polyclonal immune response against some autoantigens [23]. In light of these data, elevated serum thyroid antibody levels may be seen as the representatives of altered immunity. Consequently, removal of the thyroid gland alone cannot improve the quality of life unless the thyroid is the major stimulating factor for autoimmunity. Dardano et al. [24] recently accounted for the possible role of thyroid autoimmunity in the HT-associated clinical syndrome. They reported fibromyalgia in one-third of their HT patients and fibromyalgia was higher in euthyroid patients. Additionally, an electron microscopic study of the skeletal muscles of euthyroid HT patients revealed alterations indicating an association with thyroid autoimmunity and muscle symptoms. This study implies that clinical course of HT patients may be more complicated than it appears and systemic autoimmunity triggered by thyroid antibodies may be the key concept. In the study by Rotondi et al. [25], it was revealed that antibody-negative HT patients have a milder clinical course, with less overt hypothyroidism, as compared to antibody-positive patients. Therefore, the poor HRQoL of euthyroid patients with a positive antibody makes it obvious that thyroid antibodies are the markers for the consequent systemic autoimmune disease development with numerous symptoms.

Thyroid hormones are essential in the nervous system development and the thyroid hormone alterations may lead to central nervous system malfunctions, such as mood and cognition disorders [12]. In our study, the mental dimensions in the SF-36 questionnaire, such as the mental health and mental composite scores, are not significantly correlated with the thyroid function tests. Concurrently, euthyroid HT patients have also been associated with the increasing risk of depression, depending on the high anti-TPO levels [11,26]. Consistent with these results, the mental health and mental composite scores especially were found to be negatively correlated with both the anti-Tg and anti-TPO levels, in our study. Patients with higher antibody levels were found to have a lower HRQoL.

Nearly, 62% of the patients were under thyroid hormone supplementation, in both the antibody negative and positive groups. It is well known that the thyroid hormone levels frequently fluctuate in HT patients and the adjustment of hormone supplementation may often be difficult [7]. Thus, the idea that patients with higher antibody levels may have experienced temporary hypothyroidism

much more than antibody-negative patients cannot be denied. This may be another contributing factor of the lower HRQoL scores in patients with higher antibody levels.

Selenium is another noteworthy subject in HT patients. Selenium deficiency is known to be associated with increased risk of cancer and infections and serious neurological diseases such as Alzheimer's and Parkinson's disease. Additionally, selenium deficiency has also been shown to contribute to mood changes, behavior, and cognitive function alterations in HT patients [27,28]. After selenium supplementation, a decrease in anti-TPO levels was revealed by Gärtner et al. [29]. Selenium is thought to affect body immune responses directly by incorporation into some selenoproteins [30]. Therefore, selenium may be a treatment option for HT patients. However, further studies are needed in this area.

In conclusion, our study revealed that higher antibody levels are negatively correlated with quality of life scores. Thus, patients who have higher anti-TPO and anti-Tg levels have significantly lower quality of life domain scores. As all our HT patients were euthyroid, the thyroid hormone supplementation rates were similar in each group. We believe that apart from hypothyroidism, a high antibody level is one of the contributing factors for the development of HT-associated symptoms leading to a lower quality of life. Other probable contributing factors such as selenium deficiency, thyroid hormone fluctuation, and disease awareness must also be kept in mind. Further studies are needed to pave the way for new approaches and treatment strategies for HT patients.

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