Is thyroid autoimmunity itself associated with psychological well-being in euthyroid Hashimoto’s thyroiditis?

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Abstract. Recent studies imply that euthyroid Hashimoto’s thyroiditis (HT) might be related with impaired HRQoL, depression and anxiety. Ninety three patients with euthyroid HT and 31 age- and gender-matched euthyroid control subjects were enrolled into this study. SF-36 questionnaire, Beck Depression Inventory and Beck Anxiety Inventory tests were used for evaluating HRQoL, depression and anxiety. Beck Depression Inventory scores were higher in patients with HT compared to control subjects (7.5 (4.0-14.75) vs. 5.0 (2.25-9.0), p=0.008). Beck Anxiety Questionnaire scores were also higher in patients with HT than controls (9.50 (5.0-17.0) vs. 5.0 (2.0-11.75), p=0.021). In SF-36 questionnaire; physical functioning (26.0 (20.0-28.0) vs. 29.0 (26.0-30.0), p=0.038), general health (16.4 (13.4-20.4) vs. 19.4 (16.3-21.2), p=0.026) and mental health (20.5 (16.0-23.0) vs. 23.0 (21.0-25.0), p=0.001) scores were lower in patients with HT than control subjects. There were no significant differences between patients with HT under levothyroxine replacement therapy compared to those without therapy in terms of depression and anxiety scores and components of SF-36 questionnaire. Beck Depression Inventory scores were positively correlated with TSH (r=0.250, p=0.01). In SF-36, role physical (r=0.192, p<0.05) and vitality (r=0.181, p<0.05) were positively correlated with fT4. Role emotional was negatively correlated with TSH (r=-0.185, p<0.05) and anti-TPO (r=-0.234, p<0.05). Mental health was negatively correlated with anti-TPO (r=-0.287, p<0.01). HRQoL is impaired and depression and anxiety scores are high in patients with euthyroid HT independent of levothyroxine replacement. Therefore, our results indicate that thyroid autoimmunity itself may have an impact on psychological well-being in euthyroid patients with HT.

Key words: Hashimoto’s thyroiditis, Depression, Anxiety, Quality of life, Autoimmunity
Materials and Methods

This cross-sectional study included 93 patients with euthyroid HT and 31 age- and gender-matched euthyroid control subjects. HT was diagnosed on the basis of positive thyroid antibodies and thyroid ultrasound features. All of the patients with HT were in euthyroid state at least for 3 months. The patient group consisted of two subgroups: euthyroid HT without medication group (LT4 (-) HT), (n=49) and euthyroid HT under levothyroxine replacement group (LT4 (+) HT), (n=44). No subjects had acute or chronic disease or were on medications that might affect thyroid function tests. The euthyroid control group was selected from healthy people without any complaints/systemic diseases who were the relatives of hospital staff without history of any thyroid disease, any symptoms or findings associated with thyroid disease and negative thyroid autoantibodies. History of previous thyroid surgery for any reason, history of malignancy, history of mental or psychiatric disease, drugs that can affect mood or cognition were the exclusion criteria.

SF-36 questionnaire, Beck Depression Inventory and Beck Anxiety Inventory tests were used for evaluating HRQoL, depression and anxiety [13-15]. After taking informed consent, all the forms were self-completed by participants. SF-36 questionnaire scores were calculated separately according to the health parameters as previously described. The study was approved by the local Institutional Review Board.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows v21.0 (IBM Corp.). Numeric variables were presented as “mean ± standard deviation” or median [25th, 75th percentiles] values. Normality of the distribution was investigated with Shapiro Wilks test. Continuity corrected chi-square test was used to evaluate the gender differences between the groups. The differences between independent groups in terms of numerical variables were examined using the t-test or the Mann Whitney U-test, according to provide the condition of parametric or nonparametric distribution. Spearman correlation analysis was performed to evaluate the relationship between variables. Post-hoc power analysis was calculated for the statistically significant variables. p value of <0.05 was considered statistically significant.

Results

Patients with HT vs. control subjects

As shown in Table 1, there were no differences in terms of age [42.0 (29.0-52.0) vs. 39.5 (27.0-55.0) years, p=0.733] and gender (86% vs. 71% female, p=0.103) between HT and control groups. TSH levels were higher (2.40±1.20 vs. 1.78±0.86 µIU/mL, p=0.010) in the HT group than control subjects (Table 1). There was no difference in fT4 levels between HT and control groups (1.20 (1.0-1.30) vs. 1.26 (1.06-1.34) ng/dL, p>0.05).

Beck Depression Inventory scores were higher in patients with HT compared to control subjects (7.5 (4.0-14.75) vs. 5.0 (2.25-9.0), p=0.008), (Table 2). Also, Beck Anxiety Questionnaire scores were higher in patients with HT than controls (9.50 (5.0-17.0) vs. 5.0 (2.0-11.75), p=0.021). Although not statistically significant, 17.3% of patients had clinically relevant depression (BDI score >17), comparing to 3.3% of participants in control group (p=0.06). Also, 58.2% of patients had at least mild anxiety which was 41.3% in control group (p>0.05).

Among the eight health parameters of SF-36 questionnaire; physical functioning (26.0 (20.0-28.0) vs. 29.0 (26.0-30.0), p=0.038), general health (16.4 (13.4-20.4) vs. 19.4 (16.3-21.2), p=0.026) and mental health (20.5 (16.0-23.0) vs. 23.0 (21.0-25.0), p=0.001) scores were lower in patients with HT than control subjects (Table 2). There were no differences between the remaining health parameters of SF-36 questionnaire including role physical, bodily pain, vitality, social functioning and role emotional scores of patients with HT and control subjects (p>0.05). For the difference between HT and control groups; the power of Beck depression was 93.5%, Beck anxiety 68.9%, physical function 17%, general health 66%, mental health 96.9% in post-hoc power analysis.

LT4 (+) HT vs. LT4 (-) HT

There were no differences in terms of gender and age between LT4 (+) HT and LT4 (-) HT groups (p>0.05). TSH levels (2.10±1.05 vs. 1.78±0.86 µIU/mL, p=0.021) were lower and fT4 levels (1.20 (1.12-1.35) vs. 1.13 (1.0-1.23) ng/dL, p=0.000) were higher in LT4 (+) HT compared to LT4 (-) HT group (Table 1). There were no statistically significant differences between LT4 (-) HT and LT4 (+) HT in terms of depression and anxiety scores and components of
Well-being in thyroid autoimmunity

Well-being in thyroid autoimmunity

thyroidism which is related to mainly thyroid dysfunction [16]. In recent years, it has been proposed that euthyroid HT is related to cognitive and affective disturbances [17]. HRQoL has been suggested to be impaired despite an euthyroid state in thyroid disorders [7]. There is some evidence that the presence of circulating thyroid specific antibodies may affect psychological well-being in euthyroid subjects with HT [6, 18]. Müssig et al. reported that high anti-TPO antibodies are associated with impaired HRQoL in euthyroid patients with HT [18]. In that study, all patients were under levothyroxine treatment which is different from our study. On the other hand, Ott et al. [6] evaluated euthyroid female patients undergoing thyroid surgery for benign thyroid diseases and they found that euthyroid female patients with high anti-TPO levels were associated with low HRQoL scores compared to euthyroid female patients with low anti-TPO levels. They concluded that patients with HT have reduced HRQoL scores independently from hypothyroidism.

SF-36 questionnaire (Table 2). As all the sub-analyses between LT4 (+) HT and LT4 (-) HT subgroups were not statistically significant, we did not perform post-hoc power analysis.

In the whole group, Beck Depression Inventory scores were positively correlated with TSH (r=0.250, p=0.01). There was no correlation between Beck Anxiety Inventory scores and thyroid function tests (p>0.05). In SF-36, there were no correlations between physical functioning, pain, general health, social functioning and thyroid function tests (p>0.05). Role physical (r=0.192, p<0.05) and vitality (r=0.181, p<0.05) were positively correlated with fT4. Role emotional was negatively correlated with TSH (r=-0.185, p<0.05) and anti-TPO (r=-0.234, p<0.05). Mental health was negatively correlated with anti-TPO (r=-0.287, p<0.01).

### Discussion

Our main finding was that HRQoL is impaired in euthyroid patients with HT compared to euthyroid control subjects. HRQoL scores have been reported to be significantly reduced in hyperthyroidism and hypothyroidism which is related to mainly thyroid dysfunction [16]. In recent years, it has been proposed that euthyroid HT is related to cognitive and affective disturbances [17]. HRQoL has been suggested to be impaired despite an euthyroid state in thyroid disorders [7]. There is some evidence that the presence of circulating thyroid specific antibodies may affect psychological well-being in euthyroid subjects with HT [6, 18]. Müssig et al. reported that high anti-TPO antibodies are associated with impaired HRQoL in euthyroid patients with HT [18]. In that study, all patients were under levothyroxine treatment which is different from our study. On the other hand, Ott et al. [6] evaluated euthyroid female patients undergoing thyroid surgery for benign thyroid diseases and they found that euthyroid female patients with high anti-TPO levels were associated with low HRQoL scores compared to euthyroid female patients with low anti-TPO levels. They concluded that patients with HT have reduced HRQoL scores independently from hypothyroidism.

### Table 1 Baseline characteristics of the study groups

<table>
<thead>
<tr>
<th></th>
<th>HT</th>
<th>Control</th>
<th>p</th>
<th>LT4 (-) HT</th>
<th>LT4 (+) HT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>93</td>
<td>31</td>
<td></td>
<td>49</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>42.0 (29.0-52.0)</td>
<td>39.5 (27.0-55.0)</td>
<td>0.733</td>
<td>39.0 (28.0-54.0)</td>
<td>45.0 (31.0-52.0)</td>
<td>0.200</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>80/13</td>
<td>22/9</td>
<td>0.103</td>
<td>42/7</td>
<td>38/6</td>
<td>1.000</td>
</tr>
<tr>
<td>TSH</td>
<td>2.40 ± 1.20</td>
<td>1.78 ± 0.86</td>
<td><strong>0.010</strong></td>
<td>2.67 ± 1.27</td>
<td>2.10 ± 1.05</td>
<td><strong>0.021</strong></td>
</tr>
<tr>
<td>fT4</td>
<td>1.20 (1.0-1.30)</td>
<td>1.26 (1.06-1.34)</td>
<td>0.218</td>
<td>1.13 (1.0-1.23)</td>
<td>1.20 (1.12-1.35)</td>
<td><strong>0.000</strong></td>
</tr>
</tbody>
</table>

HT, Hashimoto’s thyroiditis. * Statistically significant.

### Table 2 Anxiety, depression and HRQoL scores of the study groups

<table>
<thead>
<tr>
<th></th>
<th>HT</th>
<th>Control</th>
<th>p</th>
<th>LT4 (-) HT</th>
<th>LT4 (+) HT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck Anxiety Inventory</td>
<td>9.5 (5.0-17.0)</td>
<td>5.0 (2.0-11.8)</td>
<td><strong>0.021</strong></td>
<td>9.0 (6.0-14.0)</td>
<td>10.0 (4.0-18.0)</td>
<td>0.817</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>7.5 (4.0-14.8)</td>
<td>5.0 (2.3-9.0)</td>
<td><strong>0.008</strong></td>
<td>7.0 (3.0-14.0)</td>
<td>8.0 (5.0-16.0)</td>
<td>0.434</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>26.0 (20.0-28.0)</td>
<td>29.0 (26.0-30.0)</td>
<td><strong>0.038</strong></td>
<td>26.0 (23.0-28.0)</td>
<td>25.0 (18.0-29.0)</td>
<td>0.781</td>
</tr>
<tr>
<td>Role physical</td>
<td>8.0 (6.0-8.0)</td>
<td>8.0 (6.3-8.0)</td>
<td>0.375</td>
<td>8.0 (6.0-8.0)</td>
<td>8.0 (6.0-8.0)</td>
<td>0.650</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>8.2 (6.1-10.4)</td>
<td>8.7 (7.4-10.4)</td>
<td>0.385</td>
<td>8.2 (6.1-10.4)</td>
<td>9.0 (6.1-11.2)</td>
<td>0.244</td>
</tr>
<tr>
<td>General health</td>
<td>16.4 (13.4-20.4)</td>
<td>19.4 (16.3-21.2)</td>
<td><strong>0.026</strong></td>
<td>16.4 (14.0-21.4)</td>
<td>17.0 (12.5-20.4)</td>
<td>0.542</td>
</tr>
<tr>
<td>Vitality</td>
<td>15.0 (12.0-19.0)</td>
<td>17.0 (11.3-20.0)</td>
<td>0.306</td>
<td>15.0 (12.0-19.0)</td>
<td>15.0 (10.0-18.5)</td>
<td>0.364</td>
</tr>
<tr>
<td>Social functioning</td>
<td>8.0 (6.0-10.0)</td>
<td>8.0 (7.0-10.0)</td>
<td>0.326</td>
<td>8.0 (6.0-10.0)</td>
<td>8.0 (6.5-10.0)</td>
<td>0.357</td>
</tr>
<tr>
<td>Role emotional</td>
<td>5.0 (4.0-6.0)</td>
<td>6.0 (4.3-6.0)</td>
<td>0.402</td>
<td>5.0 (3.0-6.0)</td>
<td>5.0 (4.0-60)</td>
<td>0.127</td>
</tr>
<tr>
<td>Mental health</td>
<td>20.5 (16.0-23.0)</td>
<td>23.0 (21.0-25.0)</td>
<td><strong>0.001</strong></td>
<td>22.0 (17.0-24.0)</td>
<td>20.0 (15.5-23.0)</td>
<td>0.221</td>
</tr>
</tbody>
</table>

HT, Hashimoto’s thyroiditis. * Statistically significant.
In our study, we showed that euthyroid patients with HT had worse HRQoL scores compared to control group in terms of physical functioning, general health and mental health.

In the present study, we found a negative correlation between anti-TPO levels and mental health as well as role emotional scores. Regarding the association between thyroid autoimmunity and psychological well-being, Blanchin et al. showed that anti-TPO antibodies bind to human cerebellar astrocytes of patients with Hashimoto’s encephalopathy [19]. Therefore, the presence of high thyroid autoantibodies may lead to some alterations in the brain which might lead to poorer psychological well-being compared to the subjects without thyroid autoimmunity. Further studies are needed to fully establish the possible effects of circulating thyroid autoantibodies on the mental functions.

Higher depression and anxiety scores were reported in patients with euthyroid HT without levothyroxine replacement compared to control subjects suggesting that presence of thyroid antibodies might increase depression and anxiety [8]. Similarly, we found higher depression and anxiety scores in euthyroid patients with HT in the present study.

TSH levels were slightly higher in HT group than control group although all the participants were in euthyroid state in our study. Higher TSH levels were also found in previous studies comparing euthyroid HT and control subjects [20]. These findings might suggest that slightly higher TSH even in the normal range might be related with impairment in psychological well-being in patients with euthyroid HT. In our study, we found that TSH level correlated positively with Beck Depression Inventory scores and negatively with role emotional. Moreover, role physical and vitality scores were positively correlated with fT4 level. A recent previous study showed that females in the lowest-normal TSH tertile had a higher risk of depressive symptoms evaluated with Beck Depression Inventory even among patients with normal TSH levels in general population [21]. In contrast, another recent paper reported that parameters of SF-36 were not dependent on serum TSH and fT4 levels in hypothyroid patients on levothyroxine treatment [22]. The reason of this controversy may come from that personal and environmental factors can affect the answers of the individuals participating in the survey.

In the literature, it has been reported that the patients who have normal TSH levels on levothyroxine replacement therapy display significant differences in their psychological well-being compared to control subjects [18]. These patients were taking levothyroxine for any reason not only for HT. In another study, decrements in health status and mood have been shown in women under TSH-suppression or replacement levothyroxine therapy when compared to healthy controls [23]. These disturbances were found to be more prominent in women taking replacement than suppressive levothyroxine therapy. On the other hand, a recent study [24] showed that even the formulations of levothyroxine such as liquid or tablet might differently influence mood states and self-perception of well-being in patients under replacement therapy after thyroidectomy. In the present study, we found that there were no differences in terms of HRQoL, depression and anxiety scores between LT4 (+) HT and LT4 (-) HT groups. In other words, impaired psychological well-being is not normalized despite levothyroxine replacement in patients with HT. To the best of our knowledge, this is the first study comparing LT4 (+) and LT4 (-) euthyroid patients with HT with respect to HRQoL, depression and anxiety.

As a limitation of the present study, it can be argued that self-knowledge of the existence of HT may affect patients’ HRQoL and psychological scores. This is partly true since the patients are easily getting information about their illness via the internet. Indeed, the name of Hashimoto itself could make the patients anxious. One can hypothesized that if the patients had not been told of their HT, or if the controls had been told they were diagnosed with HT, depression and anxiety scores between patients and controls might be even closer. Nevertheless, all the patients and controls had been informed about their medical conditions.

In conclusion, HRQoL is impaired in patients with HT independent of levothyroxine replacement. Also, depression and anxiety scores of these patients are higher than euthyroid subjects without HT. Therefore, our results indicate that thyroid autoimmunity per se may have an impact on psychological well-being in euthyroid patients with HT.

**Disclosure**

None of the authors have any potential conflicts of interest associated with this research.
References


