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ORIGINAL

The association between severity of obstructive sleep apnea and prevalence of Hashimoto’s thyroiditis

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Abstract. Obstructive sleep apnea (OSA) has long been suggested to increase the risk of development of autoimmune diseases. We investigated the prevalence of Hashimoto’s thyroiditis (HT) in 245 euthyroid individuals, who were suspected of having OSA. After polysomnography, subjects were grouped according to apnea-hypopnea index (AHI) consecutively as controls (n=27F/32M, AHI<5), mild-OSA (n=22F/37M, 5≤AHI<15), moderate-OSA (n=23F/38M, 15≤AHI<30) and severe-OSA (n=30F/36M, AHI≥30). Diagnosis of HT based on thyroid ultrasound and positivity of serum anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO) antibodies. Hashimoto’s thyroiditis was diagnosed in 32.2% of controls and in 46.8% of all OSA patients (p=0.03). Severe-OSA patients had the highest HT frequency (51.5%) compared to controls (p=0.02), mild-OSA (42.3%, p=0.03) and moderate-OSA (45.9%, p=0.05) groups. Forty-two of control subjects (71.2%) were negative for both of the anti-TPO and anti-TG, whereas 99 (53.2%) of OSA subjects were positive at least for one of them (p=0.01). HT was detected in 62% of females, 29% of males (p<0.001). Severe female OSA patients had the highest HT prevalence (73.3%), while male control subjects had the lowest (18.7%) among all groups (p<0.001). There was no significant correlation between thyroid volume and severity of OSA but isthmus thickness was significantly correlated to AHI (p<0.01, r=0.22). In conclusion, OSA patients presented higher HT prevalence parallel to severity of OSA, especially among women. These results may lead to further investigations about relation between OSA and autoimmune thyroiditis and to development of screening schemas for severe-OSA patients for early diagnosis of HT before development of hypothyroidism.

Key words: Obstructive sleep apnea, Hashimoto’s thyroiditis, Autoimmunity

OBSTRUCTIVE SLEEP APNEA (OSA) and thyroid disorders are two prevalent health problems of adult population. Obstructive sleep apnea is effecting about 2-9% of women and 4-24% of men, by aging [1, 2]. On the other hand, thyroid deficiency is the most frequent endocrine disorder which associates with a higher prevalence of OSA. While 1.5-11% of clinically diagnosed OSA patients were shown to have hypothyroidism, about 25-35% of patients with hypothyroidism were shown to have or develop OSA [3, 4]. Hypothyroidism has been denoted as a cause of secondary sleep apnea, by giving raise to mucoprotein deposition in the upper airway, decreased neural output to airway musculature, obesity and abnormal ventilatory control [5]. Although the causal relation between thyroid disorders in terms of hypothyroidism and OSA is consistent, the relation between autoimmune thyroiditis—which is the most frequent reason of hypothyroidism— and OSA have not been well established.

Hashimo’s thyroiditis (HT) is the most common autoimmune thyroid disease characterized by lymphocytic infiltration of the gland and the presence of thyroid auto-antibodies [6]. The anti-thyroid immune response begins with the activation of antigen-specific helper-T cells and once they activate, they induce cytotoxic T-lymphocytes and B-lymphocytes via cytokines [7]. The increased differentiation of T-helper 1 cells and enhanced synthesis of some particular cytokines (IL-2, IL-6, IL-12,
Study subjects participated in a detailed overnight sleep study and polysomnographic (Jaeger®, Hoechberg, Germany) records were analyzed by an expert. The diagnosis and severity of OSA was based on the latest definitions and cut-offs for apnea-hypopnea index (AHI), recommended by the American Academy of Sleep Medicine [13]. Study population was divided into groups according to AHI and the subjects who had not OSA (AHI<5) were defined as control group. Patients with OSA were grouped according to severity as mild OSA (5≤AHI<15), moderate OSA (15≤AHI<30) and severe OSA (AHI≥30).

IFN-γ, TNF-α) were shown to play a crucial role in the pathogenesis and severity of autoimmune thyroid diseases [7-10]. However, the trigger of the induction has not been well understood. On the other hand, OSA is a chronic disease shown to be associated with low grade systemic inflammation which is suggested to be induced by intermittent hypoxia [11]. Hypoxia induced cellular injury may result in up-regulation of an immune response to intracellular antigens via the exposure of antigen presenting cells and may lead to development of auto-immune diseases in OSA patients, such as Hashimoto’s thyroiditis [12]. In this cross-sectional study, we investigated the ultrasonographic features of the thyroid gland and the presence of thyroid auto-immune antibodies in euthyroid OSA patients who had not a known thyroid disease, based on rising interest in potential links of OSA’s pathogenesis with impaired auto-immune mechanisms.

Subjects and Methods

Study population

The subjects, who were suspected of having sleep disorders were evaluated with Epworth Sleepiness Scale (Johns MW, 1991) for day time sleepiness and then underwent polysomnography at Department of Sleep Disorders Center (Ankara Diskapi YB Training & Research Hospital). After analysis of the polysomnography results, total number of 300 subjects was referred consecutively to Department of Endocrinology and Metabolism during June 2010-2011. According to questionnaire 29 subjects, who had an existing metabolic or chronic disease (diabetes mellitus, hypertension, malignancy, renal/hepatic failure, thyroidal disease or an auto-immune disease), who had surgery or radiotherapy on neck region for any reason, who had been on any long term medical treatment, who had undergone imaging tests with contrast or radioactive agents within the last 6 months were eliminated. The rest of the 271 subjects were tested for routine biochemical parameters including thyroid functions and 26 patients whose test results revealed any abnormal value, were excluded. Final number of 245 subjects was enrolled for the study and was evaluated with thyroid ultrasound and was tested for anti-thyroid antibodies. The study complied with the declaration of Helsinki and was approved by the local research ethics committee. All subjects gave written informed consent.
 Statistical analyses  
Data analysis was performed by using SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). Whether the distributions of continuous variables were normally or not was determined by Shapiro Wilk test. Levene test was used for the evaluation of homogeneity of variances. While, the mean differences among groups were compared by using One-Way ANOVA, otherwise, Kruskal Wallis test was applied for comparisons of the median values. When the \( p \) value from Kruskal Wallis test statistics are statistically significant Conover’s non-parametric multiple comparison tests was used to know which group differ from which others. The difference between gender groups was evaluated by Mann Whitney \( U \) test. Nominal data were analyzed by Pearson’s Chi-square test. Degree of association between continuous variables was analyzed by Spearman’s correlation test. A \( p \) value less than 0.05 was considered statistically significant.

Results  
Study group composed of 59 subjects with mild OSA \((5 \leq \text{AHI} < 15)\), 61 with moderate OSA \((15 \leq \text{AHI} < 30)\), 66 with severe OSA \((\text{AHI} \geq 30)\), along with 59 control subjects \((\text{AHI} < 5)\) \((n=245)\). The subjects’ characteristics, comparison of ultrasonographic features and thyroid function test results are shown in Table 1. The distribution ratio of the genders among the groups were similar \((p=0.646)\). The mean age of the patients diagnosed with OSA was 47.6±9.6, while controls’ was 44.0±8.1 \((p=0.02)\), however there was no significant difference between OSA groups. While severe OSA patients had higher mean body mass index BMI \((33.6 \text{ kg/m}^2)\) compared to control group \((p<0.001)\), there was no significant difference between other control, mild and moderate OSA groups. The thyroid volume was not correlated to BMI in OSA patients and either in control subjects. On the other hand the isthmus thickness was significantly higher in OSA patients and correlated with apnea-hypopnea index as shown in Fig. 1 \((p=0.05)\).

Forty-two of control subjects \((71.2\%)\) were negative for both of the Anti-TPO and Anti-TG, whereas 99 \((53.2\%)\) of OSA subjects were positive at least for one of them \((p=0.01)\). Presence of antibody positivity was also differ among OSA groups; while 42.6% of moderate and severe OSA patients \((n=127, \text{AHI} \geq 15)\) had positive at least for one type of antibodies, 23.7% of mild OSA patients had positive Anti-TPO and/or Anti-TG. On the other hand OSA patients had

| Table 1 Subjects’ characteristics, thyroid functions and ultrasonographic features |
|-----------------|----------------|-----------------|-----------------|-----------------|-----------------|-------|
|                 | Control \((\text{AHI}<5)\) | Mild \((5 \leq \text{AHI}<15)\) | Moderate \((15 \leq \text{AHI}<30)\) | Severe \((\text{AHI} \geq 30)\) | Total | \( p \) |
| Number (n, total) | 59 | 59 | 61 | 66 | 245 | 0.647 |
| Female | 27 (45.8%) | 22 (37.3%) | 23 (37.7%) | 30 (45.5%) | 102 (41.6%) | 0.647 |
| Male | 32 (54.2%) | 37 (62.7%) | 38 (62.3%) | 36 (54.5%) | 143 (58.4%) | 0.647 |
| Anti-TPO and Anti-TG (+) | 7 | 11 | 10 | 14 | 42 | 0.05 |
| Anti-TPO or Anti-TG (+) | 10 | 14 | 15 | 15 | 54 | <0.05 |
| Anti-TPO or Anti-TG (-) | 42 | 34 | 36 | 37 | 149 | <0.05 |
| Normal Thyroid USG (n, %) | 27 (45.8%) | 18 (30.5%) | 12 (19.7%) | 11 (16.7%) | 68 (27.8%) | <0.05 |
| Hashimoto’s thyroiditis (n, %) | 19 (32.1%) | 25 (42.3%) | 28 (45.9%) | 28 (51.5%) | 106 (43.2%) | <0.05 |
| Age (mean ± SD) | 44.0 ± 8.1 | 47.3 ± 10.3 | 47.9 ± 9.4 | 47.9 ± 9.4 | 46.8 ± 9.4 | 0.05 |
| BMI (median, kg/m\(^2\)) | 27.0 | 28.8 | 30.5 | 33.6 | 30.1 | 0.01 |
| \( \text{AHI (mean ± SD)} \) | 3.5 ± 2.2 | 11.6 ± 2.9 | 23.5 ± 4.8 | 68.8 ± 25.3 | 28.0 ± 29.1 | 0.001 |
| TSH (mean ± SD, mIU/mL) | 1.9 ± 0.9 | 2.0 ± 0.9 | 2.0 ± 1.0 | 2.1 ± 1.0 | 1.9 ± 0.9 | 0.132 |
| free-T\(_4\) (mean ± SD, ng/dL) | 1.3 ± 0.1 | 1.2 ± 0.2 | 1.2 ± 0.2 | 1.2 ± 0.2 | 1.2 ± 0.2 | 0.696 |
| free-T\(_3\) (mean ± SD, pg/mL) | 3.2 ± 0.4 | 3.2 ± 0.5 | 3.2 ± 0.4 | 3.1 ± 0.4 | 3.2 ± 0.4 | 0.83 |
| Thyroid volume (mean, mL) | 17578.1 | 17431.4 | 18538.7 | 17052.2 | 17640.3 | 0.7 |
| Thyroid volume (median, mL) | 15187.9 | 15480.8 | 15655.5 | 14372.0 | 15187.9 | 0.7 |
| Isthmus thickness (mean ± SD, mm) | 3.1 ± 1.3 | 3.2 ± 1.1 | 3.4 ± 1.0 | 3.7 ± 1.2 | 3.3 ± 1.2 | 0.001 |

AHI: Apnea-hypopnea index

Normal values of thyroid function tests: TSH 0.27-4.2 mIU/mL, Anti-Thyroid peroxidase (Anti-TPO) 0-35IU/mL, Anti-Thyroglobulin (Anti-TG) 5-40 U/mL, fT\(_4\) 0.74-1.52 ng/dL, fT\(_3\) 2.3-4.2 pg/mL

\( p<0.05 \) was considered statistically significant. For thyroid volume calculation and ultrasonographic definitions, see “Subjects and Methods.”
the highest antibody levels compared to controls; as
1000 U/mL versus 400 U/mL for Anti-TG and 4490
IU/mL versus 650 IU/mL for Anti-TPO respectively.
The frequency of Hashimoto’s thyroiditis was signifi-
cantly increased in severe OSA patients (51.5%) com-
pared to control subjects (32.1%) \( (p<0.02) \). Among
OSA patients, the frequency of Hashimoto’s thyroiditis
was 45.9% and 42.3% for moderate and mild groups
respectively \( (p=0.05) \). Ultrasonographic evaluation
and laboratory results of the subjects who were diag-
nosed Hashimoto’s thyroiditis demonstrated in Table 2.
Mean age of patients with HT was 49.7 and 60.4% of
them were females, and 64.7% of severe OSA patients
with HT were females. On the other hand, frequency
of thyroiditis increased among males in moderate and
severe OSA groups \( (n=28/42, 66.6\%) \) (Table 3). Mean
thyroid volume of females was significantly lower
than male subjects \( (14315.8 \text{ mL versus } 20011.6 \text{ mL},
\ p<0.001) \). Minimum \( \text{versus} \) maximum values of thy-
roid volume for females and males are 1092.0 mL
\( \text{versus} \) 39221.9 mL and 8294.8 mL \( \text{versus} \) 66365.6 mL
respectively. While 54.9% of females had positive
Anti-TPO and/or Anti-TG, 72 % of males were neg-
ative for both of antibodies. Hashimoto’s thyroiditis
was significantly more frequent in females compared
to males \( (62.8\% \text{ versus } 29.4\%, \ p<0.001) \). Thirteen
of 64 female subjects with HT were in control group
(20.3%), however 79.7% of them were OSA patients;
33.3% of whom were mild OSA \( (n=17) \), 66.6% were
moderate-severe OSA \( (n=34) \). On the other hand, 6 of
42 male patients with thyroiditis were in control group,
while 8 of them had mild OSA \( (5\leq \text{AHI}<15) \) and 28 of
them had moderate-severe OSA \( (\text{AHI}\geq15) \).

The frequencies of other thyroid diseases in patients
with OSA and control subjects are shown in Figs. 2
and 3 respectively. Forty six percent of control group
had normal thyroid gland functions and ultrasound,
but 78% percent of OSA patients had HT, diffuse or
nodular goiter. Eighteen of 29 subjects (62%) with diff-
use goiter were moderate and severe OSA patients
with \( \text{AHI}\geq15 \). Similarly nodular goiter was observed
in 18.9% of moderate and severe OSA patients, while
16.9% and 13.6% of mild OSA and control groups had
nodular goiter. Subjects with solitary or multiple nod-
ules were also more prevalent in OSA patients com-
pared to controls \( (33.9\% \text{ versus } 39.2\% \text{ respectively}) \).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Ultrasonographic features and laboratory results of subjects with Hashimoto’s thyroiditis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (AHI&lt;5)</td>
</tr>
<tr>
<td>Number (n, total)</td>
<td>19</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
</tr>
<tr>
<td>Anti-TPO and Anti-TG (+)</td>
<td>7</td>
</tr>
<tr>
<td>Anti-TPO or Anti-TG (+)</td>
<td>10</td>
</tr>
<tr>
<td>Anti-TPO and Anti-TG (-)</td>
<td>2</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>47.37 ± 7.5</td>
</tr>
<tr>
<td>TSH</td>
<td>2.09</td>
</tr>
<tr>
<td>Thyroid volume (mean, mL)</td>
<td>16920.9</td>
</tr>
</tbody>
</table>

AHI: Apnea-hypopnea index

Normal values of thyroid function tests: TSH 0.27-4.2 mIU/mL, Anti-Thyroid peroxidase (Anti-TPO) 0-35IU/mL, Anti-
Thyroglobulin (Anti-TG) 5-40 U/mL.

\( p<0.05 \) was considered statistically significant. For thyroid volume calculation and ultrasonographic definitions, see
“Subjects and Methods.”
Obstructive sleep apnea and thyroiditis

Hashimoto’s thyroiditis is the most common type of auto-immune thyroiditis and the most frequent cause of hypothyroidism [6]. Auto-immune thyroiditis is mostly known to present with concomitant several systemic diseases, but there is not enough data about the association between Hashimoto’s thyroiditis and OSA. In this study evaluated euthyroid OSA patients for existence of auto-immune thyroid antibodies and together with the ultrasonographic evaluation we showed that Hashimoto’s thyroiditis was significantly more frequent in OSA patients parallel to increment in AHI. Similarly Erden and colleagues evaluated the subjects with Hashimoto’s thyroiditis and showed that OSA was more prevalent among those patients, in a small group [15]. There could be several explanations about this association. In Hashimoto’s thyroiditis, the anti-thyroid immune response begins with activation of thyroid antigen specific helper T cells which induce B cells to secrete thyroid antibodies, mostly directed against thyroid peroxidase and thyroglobulin [6, 7]. Although genetic disposition plays an important role in development of auto-immune thyroid diseases, the disruption of immune homeostasis by external or internal factors are involved in the induction of autoimmunity [7]. On the other hand, OSA is a chronic disease characterized by repetitive upper airway obstruction resulting in intermittent hypoxia [13]. Number of studies claimed that repetitive episodes of hypoxia followed by re-oxygenation, result in genera-

Discussion

Table 3 Comparison of male and female study subjects

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>102</td>
<td>143</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>48.9 ± 8.8</td>
<td>45.3 ± 9.6</td>
<td>0.002</td>
</tr>
<tr>
<td>BMI (kg/m²) (mean ± SD)</td>
<td>33.6 ± 8.0</td>
<td>29.2 ± 4.6</td>
<td>0.001</td>
</tr>
<tr>
<td>AHI (mean ± SD)</td>
<td>28.6 ± 28.9</td>
<td>27.6 ± 29.3</td>
<td>0.861</td>
</tr>
<tr>
<td>TSH</td>
<td>2.1 ± 1.0</td>
<td>1.8 ± 0.9</td>
<td>0.022</td>
</tr>
<tr>
<td>Anti-TPO and Anti-TG (+)</td>
<td>27</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Anti-TPO or Anti-TG (+)</td>
<td>29</td>
<td>25</td>
<td>0.001</td>
</tr>
<tr>
<td>Anti-TPO and Anti-TG (-)</td>
<td>46</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>Thyroid volume (mean, mL)</td>
<td>14315.8</td>
<td>20011.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Thyroid volume (median, mL)</td>
<td>12886.2</td>
<td>17547.7</td>
<td></td>
</tr>
<tr>
<td>Isthmus thickness (mm)</td>
<td>3.2</td>
<td>3.4</td>
<td>0.032</td>
</tr>
</tbody>
</table>

AHI: Apnea-hypopnea index

Normal values of thyroid function tests: TSH 0.27-4.2 mIU/mL, Anti-Thyroid peroxidase (Anti-TPO) 0-35IU/mL, Anti-Thyroglobulin (Anti-TG) 5-40 U/mL p<0.05 was considered statistically significant. For thyroid volume calculation and ultrasonographic definitions, see “Subjects and Methods.”

Fig. 2 The distribution of thyroid disorder frequencies in control group

Fig. 3 The distribution of thyroid disorder frequencies in obstructive sleep apnea patients
tion of reactive oxygen species which can up-regulate transcription factors that control inflammatory pathways in OSA [16-20]. Conveniently, many studies showed that the plasma levels of some pro-inflammatory cytokines elevated and cytotoxicity of γδ T-cells were higher in OSA patients [16, 20]. Increased levels of TNF-α, IL-6, IL-8 and decreased levels of IL-10 supported a prevailing activation of the Th1-type cytokine pattern in OSA patients [18]. Analysis of cytokine expression showed that Th-1 cytokines were also more prevalent in Hashimoto’s thyroiditis and the portion of peripheral Th-1 cells was higher in patients with severe HT [7, 8]. Based on evidence, those results may suggest that hypoxia induced cellular injury -as in OSA patients- accelerate the activation of antigen presenting cells and their presentation to T-cells of immunogenic molecules, some of which are self antigens. Abrams hypothesized that long term sleep apnea may increase the risk of cell mediated auto immunity via its association with hypoxia induced precipitation of monosodium urate and resulting in repeated exposure of antigen presenting cells to epitopes of intracellular origin [12]. Same mechanism may be ruling for thyrocyte antigens. All these mechanisms may inspire further investigations to explain an association between OSA and Hashimoto’s thyroiditis.

Recently, obesity was evaluated as a risk factor for development of auto-immune thyroiditis. Marzullo and colleagues claimed that obesity might increase the susceptibility to develop AIT, based on higher positivity of anti-TPO [21]. They also showed an association between AIT and plasma leptin levels but independent of obesity. On the other hand obesity is a well-known risk factor for OSA [13, 19]. In our study, BMI increased in subjects parallel to severity of OSA and increased prevalence of HT. Although adipose tissue is a well known source of pro-inflammatory cytokines, many studies showed an independent association between severity of OSA and increased levels of cytokines independent of BMI [19]. However, in this study we did not evaluate the cytokine or adipocytokine levels of the subjects. The adipocytokines IL-6 and leptin inhibit regulatory T cells, and obesity alters cell-mediated Th-1 immune response [21]. Those caveats must be kept in mind to design further studies evaluating patho-physiologic associations between OSA and HT.

Many authors advised routine screening of OSA patients for thyroid functions in order to prevent misdiagnosis of hypothyroidism, which is one of the etiologic factors of OSA and also have common clinical symptoms such as fatigue, decreased libido, depressed mood, impaired concentration, obesity and edema [3, 5, 22-24]. Recently it was suggested that these symptoms might also be related to serum antibody levels of patients with thyroiditis, even if the patient was euthyroid [25]. The presence of these antibodies was also proposed to correlate with thyroidal damage and lymphocytic inflammation [26] and euthyroid patients with higher serum antibody concentrations had progression to overt hypothyroidism at an approximate rate of 2 to 4 percent a year [27]. On the other hand, prophylactic L-thyroxin treatment was shown to decrease serum anti-TG and anti-TPO levels in euthyroid subjects with HT [28]. Resta et al. showed that sleep propensity was found to increase in untreated OSA patients with subclinical hypothyroidism [29]. Our results demonstrated that, presence of thyroid antibodies in moderate-severe OSA patients were significantly higher than control subjects. Regarding to our hypothesis, patients with subclinical hypothyroidism related to Hashimoto’s thyroiditis may be questioned for sleep disorders which may be of benefit for early diagnosis of OSA.

In conclusion, we showed that auto-immune thyroiditis (in terms of HT) was about two folds more prevalent in euthyroid OSA patients with AHI>15 and based on data, we suggest that OSA may be a pathogenic factor for thyroid auto-immunity. This association may also explain the relation between increased prevalence of hypothyroidism and OSA from another perspective. Screening of thyroid functions, not only for hypothyroidism but also for auto-immune thyroid diseases in OSA patients may be of benefit for early diagnosis a thyroid failure. On the other hand, evaluation of patients with autoimmune thyroid diseases for sleep disorders may lead to early diagnosis of OSA and prevent from long term metabolic consequences.

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Author Disclosure Statement

All of the authors of this manuscript had nothing to disclose. No competing financial interests exist.
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