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Prevalence of thyroid disease in patients with obstructive sleep apnea

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Summary
Objectives: Studies have suggested that ethnicity and environment may influence thyroid disease. We aim in this study to determine the prevalence of thyroid disease among Saudi (Arab) patients with laboratory-diagnosed obstructive sleep apnea (OSA) and the characteristics and predictors of thyroid disease associated with OSA.
Methods: Serum thyroid-stimulating hormone (TSH) and free-thyroxine (FT4) levels were measured in all patients referred to the sleep disorders center for an overnight sleep study. The levels were measured within 4 weeks of the sleep study. Type I attended polysomnography (PSG) was performed for all patients.
Results: During the study period, 271 patients with OSA and a mean age of 48.7 ± 14.1 yr, a body mass index (BMI) of 37.7 ± 9.6 kg/m^2 and an AHI of 55.2 ± 37/hr as well as 76 non-OSA patients with a mean age of 40.8 ± 14.9 yr, a BMI of 33.7 ± 8.9 kg/m^2 and an AHI of 3.8 ± 3.1/hr underwent thyroid function tests. In the OSA patients, the prevalence of newly diagnosed clinical hypothyroidism was 0.4%, and the prevalence of newly diagnosed subclinical hypothyroidism was 11.1%. In the non-OSA patients, the prevalence of newly diagnosed clinical hypothyroidism was 1.4%, and the prevalence of newly diagnosed subclinical hypothyroidism was 4%. There were no cases of clinical or subclinical hyperthyroidism in the studied group. Female gender was the only predictor of clinical hypothyroidism.
Conclusion: In the OSA patients, the prevalence of newly diagnosed clinical hypothyroidism was low; however, subclinical hypothyroidism was common among patients with OSA.

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Introduction

Hypothyroidism has been associated with obstructive sleep apnea (OSA), as some symptoms for both illnesses overlap. The proposed mechanisms for the relationship between OSA and hypothyroidism include the deposition of mucoproteins in the upper airway causing upper airway obstruction, disturbances of the regulatory control of pharyngeal dilator muscles due to neuropathy, and the possibility of respiratory center depression.[1] Thyroxine as a replacement therapy does not always resolve the sleep disordered breathing (SDB), and treating SDB does not cure hypothyroidism. Thus, the recognition and treatment of both disorders is essential.[2–5] The overlap between the two disorders may create a problem for the treating physician in differentiating both disorders and may result in a misdiagnosis or under-recognition of one of the disorders. Hypothyroid patients commonly suffer from SDB; however, previous studies have reported conflicting results, and the majority of studies have shown that hypothyroidism is relatively uncommon among OSA patients.[2,3,6–9] A prevalence of 1–10% has been reported in patients with OSA in different studies using different diagnostic criteria.[8,10–13] However, in a previous study designed to assess gender differences in Saudi patients with OSA, we found that thyroid disease prevalence was higher among women (23.6%) compared to men (6.2%).[14] Some of the previous studies defined hypothyroidism as the presence of a high serum thyroid-stimulating hormone (TSH) level without commenting on thyroxine hormone level. This means that some of the patients thought to have hypothyroidism may actually have had subclinical hypothyroidism, which carries different therapeutic and prognostic implications.[8,12,15] Several studies have suggested that both environmental factors and ethnicity influence the prevalence of hypothyroidism.[16–18] As a result, the prevalence of hypothyroidism in OSA patients may vary with race and geographical region. Therefore, this study was designed to determine the prevalence of thyroid disease based on TSH and thyroxine levels among Saudi (Arab) patients with laboratory-diagnosed OSA and to attempt to identify the characteristics and predictors of thyroid disease in OSA patients.

Methodology

In this prospective descriptive study, all consecutive patients who were referred to the sleep disorders center (SDC) for an overnight sleep study during the period from January 2009 to June 2010 were included in the study. Demographic and clinical data (history and physical examination) were obtained by a sleep medicine specialist during the initial assessment in the SDC that included questions related to sleep complaints, medical diagnoses and response scales from the Wisconsin Sleep Cohort Study questionnaire[19] that primarily addresses the presenting symptoms, sleep symptoms, medical symptoms, and other medical conditions. The Epworth Sleepiness Scale (ESS) was used for a subjective assessment of daytime sleepiness.[20] Patients with hypoventilation (defined as a difference of $\geq$10 mmHg in $EtCO_2$ (endtidal CO_2) during sleep compared to the awake supine value associated with sustained oxygen desaturation that was not associated with obstructive apneas, hypopneas or periodic breathing[21]), patients with neuromuscular diseases, acutely ill patients and those who were taking medication that might affect thyroid testing, such as amiodarone, dopamine agonists and lithium, were excluded. None of the studied patients was taking hypnotics or narcotics at the time of the study. Consent was obtained from all participants, and the study was approved by the institutional review board.

Thyroid evaluation

Serum TSH and thyroxine (FT4) levels were measured in the morning within 4 weeks of the sleep study using the electrochemiluminescence immunoassay (ECLIA) method[22] (Roche Diagnostics GmbH, Mannheim, Germany). The normal ranges for TSH and FT4 are 0.25–5.0 μIU/mL and 10.3–25.8 pmol/L, respectively. Clinical hypothyroidism was diagnosed for the following conditions: 1) if the patients had been diagnosed by the referring physician with hypothyroidism and had been on thyroxine replacement based on chart documentation (this will be termed known clinical hypothyroidism) and 2) if the TSH level was >5.0 μIU/mL and the FT4 level was <10.3 pmol/L while the patient was in the SDC (newly diagnosed clinical hypothyroidism). Subclinical hypothyroidism was defined as a serum TSH concentration > 5.0 μIU/mL when the serum FT4 level was within the reference range.[23] Clinical hyperthyroidism was defined as a TSH level < 0.25 μIU/mL and an FT4 level more than 25.8 pmol/L. Subclinical hyperthyroidism was defined as a TSH level < 0.25 μIU/mL in the presence of a normal FT4 level.[23]

Polysomnography

Standard in-lab type I polysomnography (PSG) was performed. Manual scoring of the electronic raw data was completed in accordance with established criteria, and the scorer was blind to the thyroid function results.[24] Respiratory events were defined according to the American Academy of Sleep Medicine (AASM) criteria.[24] We defined mild OSA as an AHI score from 5 to 15/h; moderate OSA as an AHI score from >15 to 30/h; and severe OSA as an AHI score greater than 30/h.[21] OSA was defined according to the International Classification of Sleep Disorders (ICSD 2005).[25]

Statistical analysis

The data were expressed as mean and standard deviation (SD) in both the text and the tables. Student *t*-tests were used to compare the means for continuous data. If the normality test failed, the Mann–Whitney test was used. For categorical data, the chi-square test was used. The results were considered statistically significant if $p < 0.05$. To explore the associations between independent factors and clinical and subclinical hypothyroidism, a preliminary analysis used a univariate logistic regression model; one explanatory variable was tested in the model at a time. Subsequently, variables with significant *p*-values were

evaluated further using a multivariate logistic regression model. SPSS (version 17; Chicago, IL, USA) was used for the analyses.

Results

Description of subjects

A total of 418 patients (62% males) were referred to the sleep disorders center from different specialties for an overnight sleep study during the study period. All the patients were evaluated by a sleep disorders specialist before undergoing overnight sleep studies. OSA was diagnosed in 325 patients (66% males). Seventy-one OSA patients declined to participate in the study. Among the 93 subjects who did not have OSA, 17 subjects declined to participate in the study. Therefore, 271 OSA patients (62% males) with a mean age of 48.7 ± 14.1 yr, a body mass index (BMI) of 37.7 ± 9.6 kg/m^2 and an AHI of 55.2 ± 37/hr; and 76 non-OSA patients (49% males) with a mean age of 40.8 ± 14.9 yr, a BMI of 33.7 ± 8.9 kg/m^2 and an AHI of 3.8 ± 3.1/hr participated in the study. The prevalence of smoking and other common chronic illnesses in the OSA patients was as follows: smoking (11.4%), hypertension (43.5%), coronary artery disease (14%), diabetes mellitus (36.2%), compensated heart failure (1.5%), and bronchial asthma (34.7%). In the non-OSA patients, the prevalence was as follows: smoking (6.6%), hypertension (35.5%), coronary artery disease (5.3%), heart failure (0%), diabetes mellitus (26.3%), and bronchial asthma (34.7%).

In the OSA patients, the TSH levels ranged from 0.01 to 44.24 (3.1 ± 3.5) μIU/mL, and the FT4 levels ranged from 8 to 28 (15.0 ± 2.6) pmol/L; for the non-OSA subjects, the TSH levels ranged from 0.16 to 15.5 (2.6 ± 2.1) μIU/mL, and the FT4 levels ranged from 1.0 to 22.0 (14.4 ± 2.8) pmol/L. Overall, the TSH levels in all study participants ranged from 0.01 to 44.24 (3.0 ± 3.2) μIU/mL, and the FT4 levels ranged from 1.0 to 28.0 (14.8 ± 2.6) pmol/L. TSH and FT4 measurements were repeated for 20 patients with subclinical hypothyroidism within 4–8 weeks of the first assessment, and the initial findings were confirmed. There was no difference in the distribution of OSA severity for the different categories of thyroid function.

Thyroid disease among subjects

Clinical hypothyroidism

Among the OSA patients, a total of 26 (9.6%) had been previously diagnosed by their treating physicians with clinical hypothyroidism and had started taking a thyroxine replacement. One (0.4%) patient was newly diagnosed at the SDC based on high TSH and low FT4 levels. The prevalences of clinical hypothyroidism among female and male OSA patients were 23.9% (21 out of 88) and 3.8% (6 of 156), respectively.

Table 1 presents a comparison of the demographic and polysomnographic data for the OSA patients with and without clinical hypothyroidism. Hypothyroid patients were heavier, had a higher prevalence of hypertension and diabetes mellitus, and spent more time with an $SaO_2 < 90$.

Table 2 presents within-gender comparisons between the OSA patients with and without clinical hypothyroidism. Male hypothyroid patients were heavier, had a higher desaturation index, and spent a longer time with an $SaO_2 < 90\%$ (34.3 ± 38.9 min vs. 13.5 ± 24.4 min, $p < 0.05$). For the female OSA patients, there were no differences between euthyroid and hypothyroid patients.

Table 3 presents a comparison between the men and women with and without clinical hypothyroidism. Euthyroid women were older and heavier than euthyroid men, had a lower minimum SaO_2, and spent more time with an $SaO_2 < 90\%$. In patients with clinical hypothyroidism, there were no differences between the genders.

Among the non-OSA patients, a total of 7 of 76 (9.2%) patients had been previously diagnosed by their treating physician with clinical hypothyroidism and had started taking a thyroxine replacement. One (1.4%) patient was diagnosed with hypothyroidism based on high TSH and low FT4 levels.

Univariate analysis identified BMI, time $SaO_2<90$ (min), hypertension, diabetes and female gender as predictors of clinical hypothyroidism. In the multivariate analysis, only female gender remained a significant predictor of clinical hypothyroidism (OR:4.74, $p = 0.006$, CI: 1.551–14.490).

Subclinical hypothyroidism

Subclinical hypothyroidism was diagnosed in 27 (11.1%) OSA patients based on high TSH and normal FT4 levels. None of these patients had symptoms or signs of hypothyroidism apart from daytime fatigue and snoring. The prevalence of subclinical hypothyroidism was 17.3% and 8.0% in female and male OSA patients, respectively. The demographic and clinical characteristics of this group revealed 13 males and 14 females, an age range from 18 to 73 years, a BMI range from 24.3 to 66.3, an AHI range from 12 to 155/h and a TSH level range from 5.04 to 21.49 μIU/mL.

No differences were found between the euthyroid OSA patients and the OSA patients with subclinical hypothyroidism in either gender. The female OSA patients with subclinical hypothyroidism had a higher BMI compared to the male patients (Table 3).

In the non-OSA patients, three females were diagnosed with subclinical hypothyroidism (4%). The demographic and clinical characteristics of this group revealed that the ages ranged from 20 to 47 years, the BMI ranged from 23 to 40.8; the AHI ranged from 0 to 5/hr and the TSH level ranged from 5.84 to 9.77 μIU/mL.

Logistic regression analysis demonstrated that none of the variables studied could predict the presence of subclinical hypothyroidism.

There were no cases of clinical or subclinical hyperthyroidism in the studied group. Three patients in the OSA group and three patients in the non-OSA group had TSH levels less than 0.25 μIU/mL. All those with subnormal TSH levels were on thyroxine replacement (thyroxine overdosed).

Discussion

This study showed a relatively high prevalence of subclinical hypothyroidism among Saudi patients with OSA,

Table 1 Demographics and PSG data of OSA patients with and without clinical hypothyroidism.

Characteristics	Clinical Hypothyroidism		*p*-value
	Yes ($n = 27$)	No ($n = 217$)	
Age	53.3 ± 14.4	47.8 ± 14	0.0567
BMI	43.9 ± 8.6	36.8 ± 9.3	0.0004*
ESS	10.1 ± 7	9.8 ± 6.3	0.8099
Sex (Female)	21 (77.8)	67 (30.9)	0.000*
ESS ≥ 10	11 (40.7)	94 (45.2)	0.662
Sleep Efficiency	73.9 ± 21.9	76.7 ± 17.4	0.4460
AHI	63.7 ± 40.1	53.7 ± 36.2	0.1794
Desaturation Index	41.1 ± 28.7	31.5 ± 30.4	0.1203
Time (min) $SaO_2 < 90$	33.7 ± 35	18.8 ± 30	0.0179*
Average O_2	90.6 ± 4.4	92.1 ± 6	0.1835
Arousal Index	59.3 ± 38.8	55.8 ± 33.7	0.6249
Smoking history	2 (7.4)	28 (12.9)	0.412
Hypertension	17 (63)	92 (42.4)	0.043*
Ischemic Heart Disease	6 (22.2)	27 (12.4)	0.161
Diabetes Mellitus	15 (55.6)	76 (35)	0.037*
Bronchial Asthma	11 (40.7)	72 (33.2)	0.434

*$p < 0.05$; BMI: body mass index; ESS: Epworth Sleepiness Scale; AHI: apnea-hypopnea index; CAI: central apnea index.

particularly in women. This finding is in accordance with our previous report that explored gender differences in patients with OSA and showed a high prevalence of hypothyroid disease among women. However, that study did not discriminate between clinical and subclinical hypothyroidism.[14] The overall prevalence of thyroid disease in most of the studies conducted in Western societies has been found to be lower than that reported in this study.[3,8,9,11,12] The prevalence of newly diagnosed clinical hypothyroidism was not different from previous literature; however, subclinical hypothyroidism was more prevalent in this study compared to the majority of published data. Nevertheless, these results concurred with Resta et al., who reported an 11.5% prevalence of subclinical hypothyroidism in 78 Italian patients with OSA.[9] Possible explanations for the differences in reported prevalence include the probable effect of race and environmental and socioeconomic factors.[17,18,26] Another possible cause for this disparity in prevalence is a difference in the population from which referrals came or the referral bias. Some of the previous studies that explored thyroid disease among OSA patients measured only the TSH level and considered patients with a high TSH level as hypothyroid, which did not provide any differentiation for subclinical hypothyroidism.[8,12] In this study, we divided patients with high TSH levels into clinical and subclinical hypothyroidism in a large group of OSA patients based on the FT4 level. The prevalence of newly diagnosed clinical hypothyroidism in this study is comparable to that found in the majority of previous studies. However, the prevalence of subclinical hypothyroidism was relatively high compared to previously published studies and to the non-OSA patients. In their series, Kapur et al. reported a prevalence of subclinical hypothyroidism of 1.4%, which is low compared to our results. The prevalence of subclinical hypothyroidism has exhibited racial differences; where the prevalence in American blacks was one-third that in American whites.[23] Furthermore, in this study, a different and more sensitive assay (ECLIA) was used compared to the radioimmunoassay used by Kapur et al.

Table 2 Within-gender comparison between euthyroid and clinical hypothyroid OSA patients.

Characteristics	Female		Male	
	Euthyroidism ($n = 67$)	Clinical hypothyroidism ($n = 21$)	Euthyroidism ($n = 150$)	Clinical hypothyroidism ($n = 6$)
Age (years)	54.7 ± 14.1	54.1 ± 14.4	44.7 ± 12.8	50.2 ± 15.6
BMI	43.2 ± 9.7	44.6 ± 7.7	34.1 ± 7.7*	42 ± 11.5
ESS	8.8 ± 5.9	9.5 ± 6.8	10.2 ± 6.4	12.2 ± 7.9
Sleep Efficiency	72.5 ± 19	77.8 ± 17.5	78.6 ± 16.4*	60.5 ± 31.2
AHI	52.2 ± 38.8	59.9 ± 42.6	54.3 ± 35.2	77.3 ± 29
Desaturation Index	33.4 ± 33.2	36.3 ± 26.2	30.7 ± 29.1*	57.8 ± 33.3
Time (min) $SaO_2 < 90\%$	30.8 ± 37.5	33.5 ± 34.8	13.5 ± 24.4*	34.3 ± 38.9
Minimum O_2	73.4 ± 16.6	74.1 ± 12.5	80.5 ± 12.8*	68.8 ± 20
Arousal Index	55 ± 35.9	54.1 ± 39.5	56.2 ± 32.9	77.3 ± 33.1

*$p < 0.05$; BMI: body mass index; ESS: Epworth Sleepiness Scale; AHI: apnea-hypopnea index.

Table 3 Gender differences in euthyroid, clinically hypothyroid and subclinically hypothyroid OSA patients.

Characteristics	Euthyroid		Clinical hypothyroidism		Sub Clinical hypothyroidism	
	Male ($n = 150$)	Female ($n = 67$)	Male ($n = 6$)	Female ($n = 21$)	Male ($n = 13$)	Female ($n = 14$)
Age (years)	44.7 ± 12.8*	54.7 ± 14.1	50.2 ± 15.6	54.1 ± 14.4	52.8 ± 14.1	51 ± 13.9
BMI	34.1 ± 7.7*	43.2 ± 9.7	42.0 ± 11.5	44.6 ± 7.7	32.8 ± 6.3*	45.1 ± 11.6
ESS	10.2 ± 6.4	8.8 ± 5.9	12.2 ± 7.9	9.5 ± 6.8	8.5 ± 5.9	7.6 ± 5.3
Sleep Efficiency	78.6 ± 16.4*	72.5 ± 19	60.5 ± 31.2	77.8 ± 17.5	73.7 ± 21.5	66.7 ± 18.6
AHI	54.3 ± 35.2	52.2 ± 38.8	77.3 ± 29	59.9 ± 42.6	60 ± 33.1	57.6 ± 46.3
Desaturation Index	30.7 ± 29.1	33.4 ± 33.2	57.8 ± 33.3	36.3 ± 26.2	29.5 ± 22.9	38.7 ± 41.6
Time (min) $SaO_2<90$	13.5 ± 24.4*	30.8 ± 37.5	34.3 ± 38.9	33.5 ± 34.8	17.3 ± 29.4	27.9 ± 38.8
Minimum O_2	80.5 ± 12.8*	73.4 ± 16.6	68.8 ± 20.0	74.1 ± 12.5	82.1 ± 8.5	79.5 ± 13

*$p < 0.05$; BMI: body mass index; ESS: Epworth Sleepiness Scale; AHI: apnea-hypopnea index.

This study revealed differences between men and women with hypothyroidism. While age, BMI, respiratory parameters, the arousal index and comorbid conditions did not differ between the euthyroid and hypothyroid female OSA patients, the AHI, the desaturation index, and the time spent with an $SaO_2<90\%$ were significantly greater in the male hypothyroid OSA patients compared to the euthyroid OSA patients. Gender differences were apparent between the euthyroid men and women. Euthyroid females with OSA were older, heavier, and spent more time with an $SaO_2<90\%$ compared to the males with OSA. However, the differences were less apparent in the clinically hypothyroid group with OSA (Table 3). This suggests that women with clinical hypothyroidism may not necessarily have more severe OSA than euthyroid women. These findings concur with those of Miller et al., who reported no difference in age, BMI, the respiratory disturbance index or the arousal index between euthyroid and hypothyroid women for a group of 118 women with OSA.[12]

Currently, no evidence exists of any long-term benefit for replacement therapy in patients with subclinical hypothyroidism with regard to survival or cardiovascular morbidity.[15,23,27] Nevertheless, available data indicate that thyroxine replacement may be beneficial in certain conditions, such as resulting in the improvement of some parameters of lipid profiles and left ventricular function.[27] Studies that assessed the effects of replacement therapy in OSA patients with clinical hypothyroidism demonstrated clear benefits in nonobese patients.[1] In contrast, the improvement was less impressive in obese patients.[1] However, the effect of treating subclinical hypothyroidism in OSA patients has not yet been thoroughly assessed. A small study that examined the effects of treating subclinical hypothyroidism in patients with OSA reported no changes in the PSG parameters.[28]

Bronchial asthma prevalence among OSA patients in this study was relatively high. Nevertheless, asthma is common among Saudis and a previous study estimated the prevalence of asthma among Saudi OSA patients as 35.1%.[29,30] Another interesting finding of this study is the high diagnostic yield of PSG in patients with clinical suspicion of OSA. Around 78% of the patients suspected clinically to have OSA were confirmed to have OSA using PSG. This finding concurs with previous studies; however, it has not been stressed or discussed previously.

One limitation of the studies that assessed the prevalence of subclinical hypothyroidism in OSA patients is that they did not account for the possibility of transient subclinical hypothyroidism. Repeating the TSH and FT4 measurements after 2—12 weeks may exclude some patients with transient hypothyroidism and result in a lower number of patients initially considered to have subclinical hypothyroidism. We have repeated the thyroid function measurements for most (20 patients) but not all patients.[31]

In summary, our results suggest that the prevalence of newly diagnosed cases of clinical hypothyroidism is too low in OSA patients to warrant routine testing for thyroid function. In contrast, subclinical hypothyroidism was common among patients with OSA; however, the benefit of treating this condition is uncertain. Therefore, we do not recommend routine thyroid function testing in OSA patients unless hypothyroidism is suspected on the basis of symptoms and physical signs.

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Conflict of interest statement

We state that we have no conflict of interest to report. The project has been approved by our institutional review board and consents were obtained from all participants.

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