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Early View

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Aysegul Gencer, Ersan Atahan, Pinar Kadioglu, Birsen Mutlu

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Investigation of the frequency of obstructive sleep apnea syndrome in patients with subclinical hypothyroidism

Short title: Frequency of OSAS in subclinical hypothyroidism

Aysegul Gencer[1], Ersan Atahan[1], Pinar Kadioglu[2], Birsen Mutlu[1]

[1]Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Pulmonary Diseases, Istanbul, Turkey

[2]Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Endocrinology-Diabetes and Metabolism Diseases, Istanbul, Turkey

Corresponding author: Aysegul Gencer, Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Pulmonary Department, Koca Mustafapasa St. No:53, 34098 Fatih/Istanbul. E-mail: aysegulbozkurtgencer@gmail.com. Phone: +905413992252. ORCHID ID: 0000-0002-8365-6210

Ersan Atahan, ersanatahan@gmail.com, phone: +905337663433

Pinar Kadioglu, kadioglup@yahoo.com, phone: +905324041040

Birsen Mutlu, birsenmutlu1983@gmail.com, phone: +905323641275

Abstract

Background The aim of this study is to determine the frequency of Obstructive Sleep Apnea Syndrome (OSAS) in a study group with the diagnosis of subclinical hypothyroidism and in a control group without the diagnosis of subclinical hypothyroidism. This study compares these two groups in terms of demographic characteristics, chronic diseases, and especially polysomnographic data.

Methods A total of 120 patients were included in this study. They consistedof 60 patients with newly diagnosed subclinical hypothyroidism, and a control group of 60 patients with normal thyroid functions. Demographic, anthropometric, polysomnography data, and Epworth sleepiness scale scores of the patients were recorded and compared.

Results Any significant difference in the frequency and severity of OSAS was not detected. A significant difference was found in the oxygen desaturation index (ODI), the apnea-hypopnea index (AHI) in REM sleep, the AHI in supine sleep position, and the arousal index of the group experiencing subclinical hypothyroidism with OSAS.

Conclusion This study showed that there was no increase in OSAS frequency in patients with subclinical hypothyroidism, but it demonstrated that the ODI and the arousal index were significantly increased in OSAS patients diagnosed with subclinical hypothyroidism. It is thought that the diagnosis and treatment of OSAS in these patients may be important in preventing cardiovascular complications.

Keywords: obstructive sleep apnea syndrome, subclinical hypothyroidism, oxygen desaturation index, arousal index

Introduction

Obstructive Sleep Apnea Syndrome (OSAS) is characterized by recurrent restriction or collapse of the upper airway during sleep causing reduction or cessation of airflow in the upper respiratory tract during sleep [1]. It is a syndrome with symptoms such as snoring, excessive daytime sleepiness, and fatigue [2, 3]. OSAS is a disease that is common among middle-aged and older adults, and it affects 26% of individuals between the ages of 30 and 70 in the U.S [4]. In Russian citizens, this rate is 48.9% [5]. In 2020, Peñafiel et al. found this rate to be 49% [6]. In the study conducted by Benjafield AV et al. on the first global estimate of the prevalence of OSAS, it was stated that approximately 1 billion adults aged 30-69 years worldwide may have obstructive sleep apnea, while this number is approximately 425 million with moderate to severe obstructive sleep apnea [7]. OSAS also varies by race/ethnicity, sex, and obesity status. It is associated with many systemic diseases and carries a mortality risk. OSAS prevalence is as high as 40% to 80% in patients with cardiovascular diseases [3, 8].

The association of hypothyroidism with OSAS has been reported at rates varying between 1.2% and 11% [9, 10]. It is thought to be related to multifactorial pathways such as mucoprotein accumulation in the upper respiratory tract, decreased response of upper respiratory tract muscles to neural stimulation, and obesity [11-14].

There is less data regarding the frequency of OSAS in patients with subclinical hypothyroidism. It is thought that subclinical hypothyroidism may increase the frequency of OSAS due to a similar pathophysiology with hypothyroidism.

In this study, the aim was to investigate the frequency and severity of OSAS in patients with subclinical hypothyroidism who describe symptoms in terms of OSAS.

Methods

Study Design and Study Population

The study protocol was planned as a prospective case-control study. 120 patients who applied to the sleep unit outpatient clinic or endocrinology-diabetes and metabolism outpatient clinic between January 1, 2017 and December 31, 2017, were chosen to be included in this study.

This study was approved by our Faculty Clinical Research Ethics Committee (no.23786662-604.01.01-69643).

Participants

Study Group

Inclusion criteria:

- The patients who applied to the endocrinology outpatient clinic
- Diagnosed with untreated subclinical hypothyroidism
- Having OSAS symptoms (snoring, apnea, daytime sleepiness, etc.)
- Provided their written and undersigned voluntary consent forms
- Between the ages of 18 and 85
- Not using medications that could interfere with thyroid function (lithium, amiodarone, corticosteroids) nor taking the thyroid-stimulating hormone (TSH) assay

Exclusion criteria:

- Patients with a diagnosis of malignancy, chronic kidney disease, heart and liver failure
- Pregnancy
- Having insufficient sleep time or technically unsuitable for polysomnography

Control group

Inclusion criteria:

- The patients who applied to the sleep unit outpatient clinic
- Having normal serum TSH, free thyroxine (T4), and free triiodothyronine (T3) levels
- Not using medications that could interfere with thyroid function

- Having OSAS symptoms (snoring, apnea, daytime sleepiness, etc.)
- Provided their written and undersigned voluntary consent forms
- Between the ages of 18 and 85

Exclusion criteria:

- Patients with a diagnosis of malignancy, chronic kidney disease, heart and liver failure
- Pregnancy
- Having insufficient sleep time or technically unsuitable for polysomnography

Data Collection

Among the demographic and anthropometric variables planned to be examined in the study, age, gender, smoking, various comorbidities (hypertension, diabetes, coronary artery disease, asthma, chronic obstructive pulmonary disease), BMI and neck circumference were performed at the screening visit. Neck circumference was measured in cm from the level of the cricothyroid membrane. Serum TSH, free T4, and free T3 levels were analyzed in patients on an empty stomach 2 times at 3-6 month intervals at least, and patients diagnosed with subclinical hypothyroidism were identified, polysomnography appointment was given to these patients.

Subclinical hypothyroidism: It is a biochemical definition in which TSH is found to be higher while thyroid hormone levels are normal at the tissue level without obvious symptoms of hypothyroidism. Subclinical hypothyroidism is asymptomatic most of the time. Rarely, symptoms of hypothyroidism may occur: Dry skin, hair loss, constipation, hypertension, bradycardia, muscular weakness, fatigue, irregular periods [15].

The Epworth Sleepiness Scale (ESS) was applied to each patient, scored, and the results during 8 hours of monitoring throughout the night were recorded. ESS scores of 10 and above were considered daytime sleepiness.

Polysomnography (PSG) data: The minimum requirements for PSG are based on the recording protocol from the American Association of Sleep Medicine (AASM) 2007 report. Monitorizations were performed using EEG (C3 / A2, C4 / A1, Fp1 / A1, Fp2 / A2, O1 / A1, O2 / A2), EOG (right and left), chin, and 2 legs EMG, ECG, nasal cannula, thermistor, tracheal microphone, body position, oximetry, and respiratory effort channels.

PSG recordings were made using the SOMNOscreen plus system (SOMNOmedics GmbH, Randersacker, Germany).

The PSG result of each patient was scored by the same person in accordance with the standards. The AASM 2012 scoring criteria were used. The AASM 2013 hypopnea recommended criteria were used for the scoring of hypopneas: required a ≥3% decline in oxygen saturation accompanied by a ≥30% decline in the amplitude of the nasal airflow.

The AASM has outlined the clinical and sleep testing criteria for OSAS in the third edition of the International Classification of Sleep Disorders [16]. The severity of OSAS can be classified according to the number of respiratory events observed per hour, termed the Apnea Hypopnea Index (AHI): mild OSA (AHI 5–14.9/hour), moderate OSA (AHI 15–29.9/hour), and severe OSA (> 30/hour) [17].

The Oxygen Desaturation Index (ODI) was calculated as the number of oxygen desaturations per hour during the total sleep time. 3% desaturation was used.

Statistical Analysis

The SPSS 25.0 IBM package program was used for analysis. Categorical data were expressed as frequency and percentage, while numerical variables were summarized with mean ± standard deviation and median (1st-3rd quartile) values. The chi-square test was used to compare categorical variables between groups. The compliance of continuous numerical variables to normal distribution was evaluated using the Shapiro-Wilk test.

For pairwise comparisons of the groups, the patient's t-test was used for numerical

variables with normal distribution, and Mann- the Whitney U test was used for non-normally distributed variables.

The Spearman Correlation test was used to examine the correlation between numerical variables. A $p < 0.05$ was accepted as the limit of statistical significance.

To identify important factors of subclinical hypothyroidism, evaluations were made by using the backward stepwise likelihood ratio multiple logistic regression analysis.

Results

The demographic and clinical characteristics of the two groups are shown in Table 1. The median total of time that the patient smoked was found to be higher in the control group.

The ESS scores and the AHI values of the patient group with subclinical hypothyroidism and the control group were similar ($p = 0.908$). 54 (90%) patients in the subclinical hypothyroidism group and 56 (93.3%) patients in the control group were diagnosed with OSAS. It was also observed that OSAS severity distributions were similar ($p=0.785$). In the study group, 11 (18.3%) patients were mild, 23 (38.3%) moderate, 20 (33.3%) severe; in the control group, 14 (23.3%) patients were mild, 20 (33.3%) moderate, 22 (36.7%) severe OSAS.

Compared with the control group, the study group's total sleep duration ($p = 0.021$), AHI in REM sleep ($p = 0.041$), AHI in supine sleep position ($p = 0.016$), and the arousal index ($p = 0.047$) were statistically and significantly more, and stage 1 sleep duration ($p = 0.009$) was statistically and significantly lower. The ODI of the study group was higher than the control group (Table 2) (Figure 1).

We performed multiple logistic regression analyses to determine significant factors of the subclinical hypothyroidism. We found female gender ($p=0.023$), higher min SO_2 values ($p = 0.007$), and higher ODI values ($p = 0.004$) are associated subclinical hypothyroidism.

Other variables (age, smoking time, comorbidities, BMI, ESS, AHI, nocturnal desaturation, REM-related OSA) were found as non-significant. (Table 3)

Discussion

In this study, the frequency and severity of OSAS were investigated in patients with subclinical hypothyroidism. The frequency of OSAS in patients with subclinical hypothyroidism was similar to the control group. There was no difference between OSAS severity levels. The ODI and the arousal index of patients diagnosed with subclinical hypothyroidism was found to be higher.

There are many studies on the frequency and relationship of hypothyroidism with OSAS. It has been shown that hypothyroidism accompanies 1.6 - 11% of patients with a diagnosis of OSAS [9, 10]. The prevalence of subclinical hypothyroidism has been found to vary between 8% and 17% [10,18-21]. However, there are few studies in terms of the frequency of OSAS and its relationship with subclinical hypothyroidism [9,22,23]. In this study, patients with subclinical hypothyroidism describing OSAS symptoms and the control group with OSAS symptoms were compared. There was no difference between the patient group and the control group in terms of OSAS frequency or severity.

The first study about the frequency of OSAS in patients with subclinical hypothyroidism was conducted by Resta et al. In that study, the control group and the small number of subclinical hypothyroidism patients who received and did not receive thyroxine treatment were compared. There wasn't a significant difference between these groups in terms of OSAS prevalence, oxygen saturation, or the ODI [24]. In our study, a larger sample of 60 untreated patients with subclinical hypothyroidism was compared, and the ODI was found to be significantly higher in the group diagnosed with subclinical hypothyroidism.

There is a multifactorial pathogenesis in the relationship between hypothyroidism and OSAS. Increased cytokines, such as IL-6 and TNF-α and subclinical inflammation, are

likely due to oxidative distress [25-27]. Impairment of tissue oxygenation causes down-regulation of deiodinase-1 activity and induction of deionidase-3 activity. This means there is a decrease in thyroid hormone production and an increase in deactivation [28]. In addition, obesity, myxedema in the upper airways, changes in myosin heavy chain expression in the pharyngeal dilator muscles, and dysregulation at the level of chemoreceptors and depression in the respiratory center are possible mechanisms thought to cause OSAS in hypothyroid patients. The main pathophysiological determinant appears to be pharyngeal narrowing due to soft tissue infiltration by mucopolysaccharides and proteins in the context of generalized infiltration of the skin and soft tissues, a well-known feature of hypothyroidism. Depression of respiratory centers may also theoretically be involved [29, 30]. Since there is a change in upper respiratory tract neuromotor control in REM sleep, it was thought that the increase in REM AHI in patients with subclinical hypothyroidism in our study was related to this [31]. It is an expected result that the increase in supine-AHI increase with these pathophysiological mechanisms. In our study, while the AHI was similar between groups, the ODI was found to be higher in patients with subclinical hypothyroidism. Thyroid hormone levels may change as a result of impaired tissue oxygenation due to OSAS. On the other hand, hypoxia may be increased due to inflammation caused by hypothyroidism, More studies are needed in terms of the pathogenesis of OSAS and hypothyroidism.

In a study conducted to evaluate the frequency of nonthyroidal illness syndrome and subclinical hypothyroidism in patients with a diagnosis of moderate to severe OSAS, the rate was found to be 10.4% and 8% respectively. The oxygen desaturation was more pronounced in the group with nonthyroidal illness syndrome [32]. However, in our study the ODI increased in patients with subclinical hypothyroidism.

In our study, multiple regression analysis was performed to show that the AHI values were almost the same and that the ODI averages were significantly and statistically

different. In the meta-analysis published by Zhang et al., including 12 studies and five case reports, data of 192 patients diagnosed with OSAS and hypothyroidism with OSAS showed that the prevalence of subclinical hypothyroidism was reported as 11%. It was emphasized that the ODI was significantly higher in the non-euthyroid group relative to the euthyroid group. It has been understood that the increase in desaturation, which is thought to be secondary to hypothyroidism, increases the severity of OSAS [33]. These findings support our data. In addition, in the regression analysis, female gender was also found to be a risk factor for subclinical hypothyroidism. There are data showing that hypothyroidism is six times more common in women [34].

Hypoxia has been shown in recent studies as an indicator of increased cardiovascular disease risk [8]. In our study, it was observed that OSAS patients with a diagnosis of subclinical hypothyroidism were more desaturated. In these patients, the risk of cardiovascular disease may be more common due to hypoxia.

Our study had some limitations. Any intergroup difference was not observed between the study and control groups as for the prevalence and severity of OSAS, BMI, and neck circumference values, and the frequency of accompanying comorbidities which conceivably overshadowed the statistical significance of multivariate analysis.

One of the strengths of this study is itspioneering approach to the rarely investigated frequency of OSAS in a larger number of patients with subclinical hypothyroidism as compared to the often common studies performed with smaller sample sizes. The fact that the ODI and the arousal index were found to be significantly higher in the patient group will also be a guide for further research.

Conclusion

Many studies have been published since the 1980s on the coexistence and relationship between hypothyroidism and OSAS. There are far fewer studies in terms of subclinical

hypothyroidism, and in these studies, the sample size is limited. It appears that hypothyroidism has a role in the pathophysiology of OSAS and that these two diseases are correlated.

Our study aimed to determine the frequency of OSAS with subclinical hypothyroidism and to investigate the ODI and the arousal index which were found to be significant in these patients. In patients with a diagnosis of subclinical hypothyroidism and OSAS, an increase in the ODI and the arousal index may cause cardiovascular comorbidities. Further research is needed in terms of the relationship between subclinical hypothyroidism and OSAS.

Statement of Ethics

The study was approved by our Faculty Clinical Research Ethics Committee (no.23786662-604.01.01-69643).

Informed consent: Informed consent was obtained from all individual participants included in this study.

Conflict of Interests

Authors declare that they have no conflict of interest related to this research study.

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This research study has not received any financial support.

Contribution by Authors

AE conceived the study. The protocol was designed by MB, KP, and AE, in collaboration. Patient inclusion and data collection were performed by KP and GA. Statistical analyses were done and analyzed by GA and AE. The first draft of the manuscript was written by GA. All authors contributed to the study with considerable critical review of the manuscript and approval of the final version.

Table 1. *Distribution of variables*

Variables	Study group (n=60)	Control group (n=60)	P value
Gender			
Female	27(45%)	26 (43%)	0.523
Male	33 (55%)	34 (57%)	
Age	50.57 ± 11.49	53.07 ± 11.55	0.237*
Pack-year smoking	10.90 ± 16.37 0 (0-15)	16.52 ± 21.29 13.5 (0-25.5)	0.032**
BMI (kg/m^2)	31.84 ± 5.65 31.25 (27.92 - 36.15)	31.89 ± 7.2 30.97 (28 - 34.7)	0.914**
BMI Category			
Obese	5 (8%)	6 (10%)	0.945
Overweight	23 (38%)	22 (37%)	
Normal	32 (53%)	32 (53%)	
Neck circumference (cm)	40.04 ± 4.03 39 (38 - 42)	40.82 ± 3.77 41 (38.25 - 43)	0.131**

Comorbidities		
Hypertension	17 (28%)	24 (40%)
Diabetes Mellitus	11 (18%)	9 (15%)
Coronary Artery Disease	5 (8%)	12 (20%)
Asthma	4 (7%)	4 (7%)
Chronic Obstructive Pulmonary Disease	2(3%)	1 (2%)

*Independent samples t test
**Mann- Whitney U test

Continuous data were expressed as mean ± standard deviation, median (1st-3rd quartile).

Table 2. *Distribution of polysomnography data*

	Study group (n=60)		Control group (n=60)		
Variables	Ort ± SS	Median (1st quartile - 3rd quartile)	Ort ± SS	Median (1st quartile - 3rd quartile)	p
ESS scores	7.4 ± 5.56	6 (3.5 - 9.5)	7.18 ± 5.19	6 (3 - 10)	0.837
OSAS Categories					0,786
Normal	6 (10%)		4 (7%)		
Mild	11 (18%)		14 (23%)		
Moderate	23 (38%)		20 (33%)		
Severe	20 (33%)		22 (37%)		
Total sleep time	349,17 ± 60,58	352 (305,5 -	345,91 ± 78,13	354 (280 -	**0,021***

(min)		397)		409)	
Stage N1 %	6,13 ± 4,88	4,4 (2,8 - 8)	7,62 ± 3,59	7,7 (4,7 - 9,4)	**0,017**
Stage N2 %	61,42 ± 11,4	59,1 (51,95 - 67,95)	59,1 ± 11,48	56,6 (49,4 - 67,5)	0,947*
Stage N3 %	20,63 ± 11,13	19,8 (13,3 - 26,9)	18,27 ± 9,53	18,65 (12,5 - 24,5)	0,203
REM sleep time (min)	46,68 ± 20,9	44 (35 - 60)	54,4 ± 33,42	45,25 (30 - 79)	0,397
REM %	13,45 ± 6,02	13,1 (10,2 - 16,3)	15,43 ± 8,07	15,75 (9,6 - 21,8)	0,116
Arousal index	15,05 ± 11,63	13,65 (7 - 20,5)	10,58 ± 9,99	9,3 (2,1 - 16,7)	**0,047**
AHI (events/hour)	28,18 ± 22,62	23,5 (12,9 - 34,35)	28,27 ± 20,82	22 (12,25- 37,9)	0,908
RDI (events/hour)	29,95 ± 24,39	19,8 (11,3 - 47,8)	40,22 ± 23,14	41,3 (17,6 - 60,2)	0,053
REM-AHI	30,81 ± 26,85	27 (6,8 - 53,9)	22,11 ± 22,81	17,9 (0 - 40)	**0,041**
Supine-AHI	14,03 ± 20,11	5,6 (1,1 - 15,3)	10,58 ± 17,42	0,2 (0 - 20,3)	**0,016**
ODI (events/hour)	26,39 ± 29,23	18,65 (6,65 - 32,65)	16,52 ± 21,29	6,55 (1,25 - 22,25)	**0,002**
Average SO2	93,33 ± 4,46	94 (93 - 95)	93,31 ± 2,67	94 (92 - 95)	0,359
Min SO2	83± 9,41	86 (83 - 89)	83 ± 9,05	86 (80 - 89)	0,695
T90%	6,65 ± 14,16	0,85 (0,2 -	9,19 ± 15,28	1,9 (0,2 -	0,320

		3,6)		9,1)	
T80%	2,27 ± 7,72	0 (0 - 0)	1,65 ± 7,57	0 (0 - 0)	0,995
Mean apnea duration (sec)	17,58 ± 7,32	15,4 (13,2 - 21,35)	18,23 ± 9,74	17,65 (12,8 - 23,9)	0,615
Mean hypopnea duration (sec)	29,34 ± 8,7	27,95 (22,25 - 34,75)	29,1 ± 6,92	28,2 (24,2 - 32,6)	0,873
MAD (sec)	26,93 ± 7,0	26,7 (20,9 - 30,85)	30,18 ± 12,97	26,9 (24,2 - 32,8)	0,347

*Independent samples (student's) t test was used. Mann-Whitney U test was used in other analyzes.

** Continuous data were expressed as mean ± standard deviation, median (1st-3rd quartile).

ESS: Epworth Sleepiness Scale, AHI: Apnea-Hypopnea Index, RDI: Respiratory Disturbance Index, ODI: Oxygen Desaturation Index, SO2: Oxygen Saturation, MAD: Mean apnea-hypopnea duration

Table 3. Significant factors of the subclinical hypothyroidism, multiple logistic regression analysis (Backward Stepwise, step 12)

	β coefficient	Standard Error	Wald	p	Exp(β)	95.0% Confidence Interval for Exp(β)	
Gender (Reference: Female)	-1.029	0.454	5.136	0.023	0.358	0.147	0.87

Min SO2	0.105	0.039	7.305	0.007	1.111	1.029	1.199
ODI	0.052	0.018	8.108	0.004	1.053	1.016	1.092
Constant	-7.704	3.457	4.966	0.026	0		

Dependent Variable: Subclinical hypothyroidism; Nagelkerke R^2=0.288

ODI: Oxygen Desaturation Index, SO2: Oxygen Saturation

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Quick Look

Current knowledge

Many studies have been published since the 1980s on the coexistence and relationship between hypothyroidism and OSAS. There are far fewer studies in terms of subclinical hypothyroidism, and in these studies, the sample size is limited.

What this paper contributes to our knowledge

This study showed that the ODI was increased in OSAS patients diagnosed with subclinical hypothyroidism. It is thought that the diagnosis and treatment of OSAS in these patients may be important in preventing cardiovascular complications associated with hypoxemia.

Figure 1. *Distribution of oxygen desaturation index values in the patient and the control groups*