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

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Shareable abstract (@ERSpublications)
Oxygen desaturation index and arousal index are increased in subclinical hypothyroidism patients with OSAS https://bit.ly/3Sh4H85

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Abstract

Background The aim of this study is to determine the frequency of obstructive sleep apnoea 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 consisted of 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 apnoea–hypopnoea index (AHI) in rapid eye movement 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.

Introduction

Obstructive sleep apnoea syndrome (OSAS) is characterised 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 USA [4]. In Russian citizens, this rate is 48.9% [5]. In 2020, Saldías Peñafiel *et al*. [6] found this rate to be 49%. In the study conducted by Benjafield *et al*. [7] on the first global estimate of the prevalence of OSAS, it was stated that ∼1 billion adults aged 30–69 years worldwide may have obstructive sleep apnoea, while this number is ∼425 million with moderate to severe obstructive sleep apnoea. 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].

Quick look

Lessons for clinicians

- Many studies have been published since the 1980s on the coexistence of 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.
- 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 hypoxaemia.

There are fewer 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 to that 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 1 January 2017 and 31 December 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:

- Patients who applied to the endocrinology outpatient clinic
- Diagnosed with untreated subclinical hypothyroidism
- Having OSAS symptoms (snoring, apnoea, daytime sleepiness, *etc.*)
- Provided their written and undersigned voluntary consent forms
- Between the ages of 18 and 85 years
- 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, apnoea, daytime sleepiness, *etc.*)
- Provided their written and undersigned voluntary consent forms
- Between the ages of 18 and 85 years

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, sex, smoking, various comorbidities (hypertension, diabetes, coronary artery disease, asthma, COPD), body mass index (BMI) and neck circumference were performed at the screening visit. Neck circumference was measured in centimetres from the level of the cricothyroid membrane. Serum TSH, free T4 and free T3 levels were analysed in patients on an empty stomach two times at 3- to 6-month intervals at least, and

patients diagnosed with subclinical hypothyroidism were identified; a polysomnography appointment was given to these patients.

Subclinical hypothyroidism 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 and 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.

The minimum requirements for polysomnography (PSG) are based on the recording protocol from the American Association of Sleep Medicine (AASM) 2007 report. Monitoring was performed using electroencephalogram (EEG) (C3/A2, C4/A1, Fp1/A1, Fp2/A2, O1/A1, O2/A2), electro-oculogram (EOG) (right and left), chin electromyogram (EMG), and EMG in two legs, 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 hypoponea recommended criteria were used for the scoring of hypopnoeas, which required a $\geqslant$3% decline in oxygen saturation accompanied by a $\geqslant$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 apnoea–hypopnoea index (AHI): mild OSA (AHI 5–14.9 events·h^{-1}), moderate OSA (AHI 15–29.9 events·h^{-1}) and severe OSA (>30 events·h^{-1}) [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 summarised with mean$\pm_{SD}$ 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 the Mann–Whitney U test was used for non-normally distributed variables.

The Spearman correlation test was used to examine the correlation between numerical variables. A value of $p<0.05$ 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 had mild, 23 (38.3%) moderate and 20 (33.3%) severe OSAS; in the control group, 14 (23.3%) patients had mild, 20 (33.3%) moderate and 22 (36.7%) severe OSAS.

Compared with the control group, the study group's total sleep duration (p=0.021), AHI in rapid eye movement (REM) sleep (p=0.041), AHI in supine sleep position (p=0.016) and the arousal index

TABLE 1 Distribution of variables

Variables	Study group	Control group	p-value
Subjects, n	60	60	
Sex, n (%)			
Female	27 (45)	26 (43)	0.523
Male	33 (55)	34 (57)	
Age years, mean±SD	50.57±11.49	53.07±11.55	0.237#
Pack-years smoking			0.032¶
Mean±SD	10.90±16.37	16.52±21.29	
Median (1st–3rd quartile)	0 (0–15)	13.5 (0–25.5)	
BMI kg·m^{-2}			
Mean±SD	31.84±5.65	31.89±7.2	0.914¶
Median (1st–3rd quartile)	31.25 (27.92–36.15)	30.97 (28–34.7)	
BMI category, n (%)			
Obese	5 (8)	6 (10)	0.945
Overweight	23 (38)	22 (37)	
Normal	32 (53)	32 (53)	
Neck circumference cm			
Mean±SD	40.04±4.03	40.82±3.77	0.131¶
Median (1st–3rd quartile)	39 (38–42)	41 (38.25–43)	
Comorbidities, n (%)			
Hypertension	17 (28)	24 (40)	
Diabetes mellitus	11 (18)	9 (15)	
Coronary artery disease	5 (8)	12 (20)	
Asthma	4 (7)	4 (7)	
COPD	2 (3)	1 (2)	

Continuous data were expressed as mean±SD and median (1st–3rd quartile). BMI: body mass index. #: independent samples *t*-test; ¶: Mann–Whitney U test.

(p=0.047) were statistically and significantly greater, 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 and figure 1).

We performed multiple logistic regression analyses to determine significant factors of the subclinical hypothyroidism. We found that female sex (p=0.023), higher minimum oxygen saturation measured by pulse oximetry (S_{pO_2}) values (p=0.007) and higher ODI values (p=0.004) are associated with subclinical hypothyroidism. Other variables (age, smoking time, comorbidities, BMI, ESS, AHI, nocturnal desaturation, REM-related OSA) were found to be 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 is present in 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* [24], in which the control group and the small number of subclinical hypothyroidism patients who received and did not receive thyroxine treatment were compared. There was not 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.

TABLE 2 Distribution of polysomnography data

Variables	Study group[#]		Control group[#]		p-value
	Mean±SD	Median (1st quartile–3rd quartile)	Mean±SD	Median (1st quartile–3rd quartile)	
ESS scores	7.4±5.56	6 (3.5–9.5)	7.18±5.19	6 (3–10)	0.837
OSAS categories, n (%)					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 min	349.17±60.58	352 (305.5–397)	345.91±78.13	354 (280–409)	**0.021**[¶]
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·h^{-1}	28.18±22.62	23.5 (12.9–34.35)	28.27±20.82	22 (12.25–37.9)	0.908
RDI events·h^{-1}	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·h^{-1}	26.39±29.23	18.65 (6.65–32.65)	16.52±21.29	6.55 (1.25–22.25)	**0.002**
Mean S_{po_2}	93.33±4.46	94 (93–95)	93.31±2.67	94 (92–95)	0.359
Minimum S_{po_2}	83±9.41	86 (83–89)	83±9.05	86 (80–89)	0.695
T90%	6.65±14.16	0.85 (0.2–3.6)	9.19±15.28	1.9 (0.2–9.1)	0.320
T80%	2.27±7.72	0 (0–0)	1.65±7.57	0 (0–0)	0.995
Mean apnoea duration s	17.58±7.32	15.4 (13.2–21.35)	18.23±9.74	17.65 (12.8–23.9)	0.615
Mean hypopnoea duration s	29.34±8.7	27.95 (22.25–34.75)	29.1±6.92	28.2 (24.2–32.6)	0.873
MAD s	26.93±7.0	26.7 (20.9–30.85)	30.18±12.97	26.9 (24.2–32.8)	0.347

Continuous data were expressed as mean±SD and median (1st–3rd quartile). ESS: Epworth Sleepiness Scale; OSAS: obstructive sleep apnoea syndrome; N1: non rapid-eye movement sleep stage 1; N2: non rapid-eye movement sleep stage 2; N3: deepest non rapid-eye movement sleep stage 3; REM: rapid eye movement; AHI: apnoea–hypopnoea index; RDI: respiratory disturbance index; ODI: oxygen desaturation index; S_{po_2}: oxygen saturation measured by pulse oximetry; T90: oxygen saturation <90%; T80: oxygen saturation <80%; MAD: mean apnoea–hypopnoea duration. [#]: n=60; [¶]: independent samples *t*-test was used, Mann-Whitney U test was used in other analyses. Bold font indicates p<0.05.

There is a multifactorial pathogenesis in the relationship between hypothyroidism and OSAS. Increased cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor-α, and subclinical inflammation are likely due to oxidative stress [25–27]. Impairment of tissue oxygenation causes downregulation of

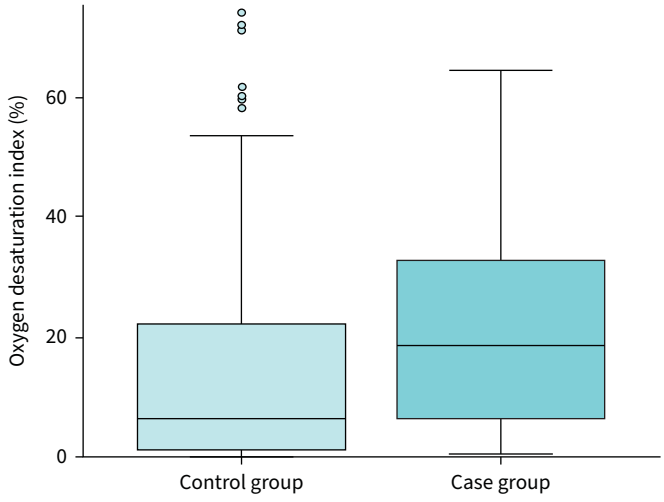

FIGURE 1 Distribution of oxygen desaturation index values in the patient and the control groups.

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

	β coefficient	Standard error	Wald	p-value	Exp(β)	95% confidence interval for Exp(β)
Sex (reference: female)	−1.029	0.454	5.136	0.023	0.358	0.147–0.87
Min S_{pO_2}	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. S_{pO_2}: oxygen saturation measured by pulse oximetry; ODI: oxygen desaturation index.

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, myxoedema 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 centre 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 generalised infiltration of the skin and soft tissues, a well-known feature of hypothyroidism. Depression of respiratory centres 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 supine AHI increases 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 but the ODI values were significantly and statistically different. In the meta-analysis published by Zhang *et al*. [33], including 12 studies and five case reports, data from 192 patients diagnosed with OSAS and hypothyroidism with OSAS showed that the prevalence of subclinical hypothyroidism was reported as 11%. It was emphasised that the ODI was significantly higher in the non-euthyroid group relative to the euthyroid group. It is 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 sex 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 to be 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 increased 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 its pioneering approach to the rarely investigated frequency of OSAS in a larger number of patients with subclinical hypothyroidism as compared to the more 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 of 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.

Provenance: Submitted article, peer reviewed.

Ethics statement: 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.

Author contributions: E. Atahan conceived the study. The protocol was designed by B. Mutlu, P. Kadioglu and E. Atahan in collaboration. Patient inclusion and data collection were performed by P. Kadioglu and A. Gencer. Statistical analyses were performed by A. Gencer and E. Atahan. The first draft of the manuscript was written by A. Gencer. All authors contributed to the study with considerable critical review of the manuscript and approval of the final version.

Conflict of interest: None declared.

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