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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

Prevalence of newly established thyroid disorders in patients with moderate-to-severe obstructive sleep apnea syndrome

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Abstract

Background Hypothyroidism can directly cause obstructive sleep apnea (OSA) but may also contribute to it through its impact on the metabolic syndrome. The purpose of this study was to establish the prevalence of known and newly diagnosed overt and subclinical hypothyroidism (SCH) among patients with OSA.

Methods We prospectively included all consecutive moderate or severe OSA patients referred for CPAP therapy. A fasting blood sample was collected to determine thyroid-stimulating hormone (TSH) and free T4 (FT4) levels.

Results A total of 280 patients were included (70% male). Mean ± SD body mass index (BMI) and apnea–hypopnea index (AHI) were 33 ± 7 kg/m^2 and 49 ± 25, respectively. Median (range) serum TSH levels and mean ± SD FT4 levels were comparable between severe and moderate OSA (1.7 (1.3–2.6) vs 2.1 (1.2–2.8); $p = 0.378$ and 15.3 ± 2.3 vs 15.3 ± 2.3; $p = 0.981$). TSH and FT4 levels were not correlated with AHI ($p = 0.297$ and $p = 0.370$, respectively), but TSH was correlated with BMI ($p = 0.049$).Of all patients, 8.9% had increased serum TSH levels (severe and moderate OSA patients had similar levels ($p = 0.711$)) and 8.2% were newly diagnosed patients (no differences were observed between severe and moderate OSA ($p = 0.450$)). A total of 16.4% of patients had some type of thyroid disorder. Thyroid function parameters were associated with BMI but not with the severity of OSA.

Conclusion In our population of moderate or severe OSA, 16% of patients had a thyroid problem and 8% of these were newly diagnosed with SCH.

Keywords Sleep-disordered breathing · Hypothyroidism · Obesity · Obstructive sleep apnea · TSH · Continuous positive airway pressure

Introduction

The prevalence of obstructive sleep apnea (OSA) is increasing and is closely related to the global obesity epidemic [1]. OSA is characterized by decreased airflow due to repetitive complete or partial obstruction of the upper airway and is associated with progressive respiratory effort to overcome the obstruction. These events are often associated with arousals and oxygen desaturation leading to sleep fragmentation and increased sympathetic neural activity [2].

In both men and women, the strongest risk factor for OSA is obesity. The prevalence of OSA increases progressively as body mass index (BMI) increases [3]. In a longitudinal study conducted in the USA, the estimated increase in prevalence of moderate-to-severe sleep disorder for the period from 1988 to 1994 and from 2007 to 2010 was 10% among 30- to 49-year-old men; 17% among 50- to 70-year-old men; 3% among 30- to 49-year-old women; and 9% among 50- to 70-year-old women [4]. In a population-based study of over 1000 adults, moderate-to-severe OSA (apnea–hypopnea index (AHI) ≥ 15/h on polysomnography (PSG)) was present in 11% of men who were of normal weight, 21% of those who were overweight (BMI 25 to 30 kg/m^2), and 63% of those who were obese (BMI >30 kg/m^2). For adult women, the trend was the same: 3% OSA for normal weight, 9% of overweight, and 22% of obese women [5].

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Thyroid and obesity are associated in two ways. First, the prevalence of thyroid dysfunction and thyroid autoimmunity is higher in obese people and, second, patients with overt hypothyroidism (OH) are more prone to gain weight compared to euthyroid patients [6, 7]. Hypothyroidism can directly cause obstructive sleep apnea (OSA) but may also contribute to it through its impact on the metabolic syndrome [8]. Although it is difficult to compare the prevalence of OSA in patients with OH between different studies, a recent systematic review paper estimated it to be between 25% and 50% [8]. Heterogeneity between studies can be due to different definitions of hypothyroidism, differences in BMI, results that were not corrected for BMI, or lack of information on the presence of goiters and/or thyroid autoimmunity. Data on the prevalence of OSA in patients with subclinical hypothyroidism (SCH) (increased serum thyroid-stimulating hormone (TSH) with normal free T4 (FT4) levels) are not conclusive [8]. Treatment of hypothyroidism with thyroid hormone supplements (LT4) can decrease AHI, but some patients need to continue with continuous positive airway pressure (CPAP) [8, 9].

In daily practice, and due to systematic screening for thyroid dysfunction in a number of clinical settings, SCH is the most commonly diagnosed type of thyroid dysfunction. SCH is not associated with a wide spectrum of symptoms compared to those observed in patients with OH [7, 10]. In large surveys performed in the USA, hypothyroidism was found in 4.6% of the population (0.3% OH and 4.3% SCH) [11, 12]. The most frequent cause of subclinical hypothyroidism is the presence of increased thyroid peroxidase antibodies (TPO-abs).

Whether or not the prevalence of thyroid dysfunction is increased in patients with OSA and whether or not these patients should be screened systematically remain controversial. In one study, the prevalence of newly diagnosed hypothyroidism was 0.4%, and the prevalence of SCH was 11.1%. In non-OSA patients, the prevalence of newly diagnosed hypothyroidism was 1.4%, and SCH was 4% [13]. In a Japanese study, the prevalence of hypothyroidism was 1.9% but the prevalence of SCH was very low (0.6%) [14]. In a recent meta-analysis, the prevalence of hypothyroidism in OSA patients was 8% and SCH was 11% [15]. Despite these recent studies showing a higher prevalence of SCH, some remain opposed to systematic screening for thyroid dysfunction, due to the many biases that are present in the studies [16].

The aim of this study was to establish the prevalence of known and newly diagnosed thyroid disorders in patients referred to the sleep lab for CPAP therapy (AHI $\geq$ 15/h on diagnostic PSG). In addition, we compared baseline characteristics and thyroid parameters between patients with moderate and severe OSA.

Methods

Patients

The study was performed in the sleep unit of the Saint-Pierre University Hospital in Brussels, Belgium (tertiary referral center). Eligible patients were aged ≥ 18 years old and recently diagnosed with OSA on the basis of a PSG showing AHI $\geq$ 15/h according to the AASM 2012 scoring rules [17]. They were sent to our sleep laboratory for initiation of CPAP therapy. Exclusion criteria were previous CPAP treatment, mixed or predominantly central sleep apnea, and language barriers or cognitive or psychiatric disorders that made informed consent difficult to obtain. All included patients provided written informed consent to participate in the study. The study protocol was approved by the Saint-Pierre University Hospital ethics committee (AK/16-01-18/4613). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Study design

This was a prospective study. All consecutive patients with at least moderate OSA referred for a CPAP titration night were included. They first underwent one fully attended CPAP titration PSG. The morning after, a fasting morning blood sample was taken. Analyses included TSH and free T4 (FT4) dosage, independently from the presence of known thyroid disorders or LT4 intake.

An increased level of TSH (> 4.2 mIU/L) with normal FT4 dosage defined SCH, while OH was present when TSH was increased and FT4 decreased under normal levels applied in our laboratory. Newly diagnosed cases of SCH and OH were considered in patients with thyroid metabolism disorders assessed by serum dosage in the absence of FT4 intake.

Serum assay

All laboratory analyses were provided by the laboratory of hormonology at our institution. Serum TSH was measured using a sandwich immunoassay with electrochemiluminescence detection on a Roche analytical platform (TSH, Roche Diagnostics). The coefficient of variation (intermediate precision) was 3.5% at 1 mIU/L. Reference values are 0.27–4.2 mIU/L (P2.5–P97.5).

Serum free T4 (FT4) was measured using a competitive immunoassay with electrochemiluminescence detection on a Roche analytical platform (FT4, Roche Diagnostics). The coefficient of variation (intermediate precision) was 3.5% at 12.8 pmol/L. Reference values are 12–22 pmol/L (P2.5–P97.5).

Statistical analysis

Data were stored in a Microsoft Excel database. Continuous data are expressed as median (min–max) when not normally distributed and as mean ± SD for normally distributed data. Categorical data are presented as number (percentage) of cases. Differences between groups (OSA with AHI< 30 and ≥ 30) were analyzed by Fisher's exact test for categorical data and by the Mann–Whitney *U* test for continuous data. Correlations between continuous variables were quantified using Spearman's ρ correlation coefficient.

All statistical tests were considered significant whenever $p < 0.05$.

Results

Between April 2016 and September 2017, 488 patients were screened and 280 included (mean age, 56 ± 13 years; mean BMI, 33 ± 7; mean AHI, 49 ± 25; 70% male). The chart of patient flow through the study is summarized in Fig. 1.

Table 1 shows demographic characteristics and thyroid function as continuous data in all patients, according to OSA severity. Serum TSH levels (median (range)) and FT4 levels (mean ± SD) in the whole study group were 1.8 (1.2–2.8) mIU/L and 15.5 ± 2.5 pmol/L, respectively. Both serum TSH and FT4 levels were comparable between patients with severe and moderate OSA. The difference between the study groups remained non-significant when adjusted for LT4 intake ($n = 25$ patients).

Table 2 shows the prevalence of altered demographic characteristics and thyroid disorders as categorical data in all patients and according to OSA severity. In the severe OSA group, the number of males and smokers was higher. The prevalence of all newly diagnosed patients with OH was 1.2%, and there was no difference between moderate and severe OSA. The prevalence of SCH was 7.0% and also comparable between the study groups, such that the prevalence of any type of thyroid disorder (newly diagnosed and established OH or SCH and patients treated with LT4) was 16.4% for the whole study group and was not affected by OSA severity.

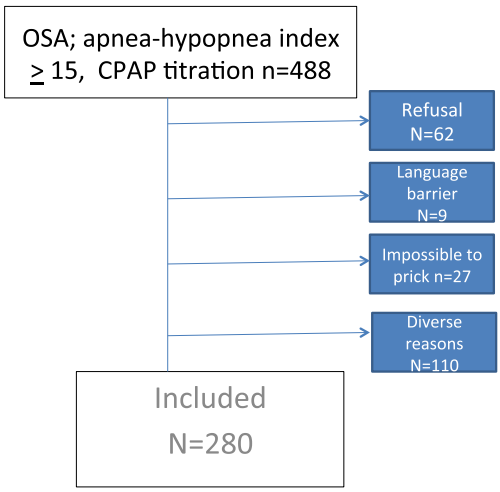

Fig. 1 The chart of patient flow through the study. *OSA* obstructive sleep apnea, *CPAP* continuous positive airway pressure

Table 3 shows the Spearman's ρ of the correlations between demographic characteristics, thyroid function parameters, and apnea–hypopnea index. AHI was correlated with BMI ($r = 0.348$; $p < 0.001$) but not with thyroid function, and BMI was correlated with TSH ($r = 0.123$; $p = 0.049$) but not with FT4.

Discussion

The primary finding from this study is the substantial prevalence of thyroid disorders in patients with OSA. These disorders included patients already treated with LT4 and those with established SCH, post-thyroidectomy, or newly diagnosed SCH.

Thyroid dysfunction (mainly OH) has been associated with a number of changes in pulmonary physiology [8]. Central apnea may also be encountered in this setting, but the main pathophysiological determinant in hypothyroidism seems to be pharynx narrowing, due to soft tissue infiltration by mucopolysaccharides and protein, in the context of the generalized infiltration of skin and soft tissue [18, 19]. Furthermore, altered regulatory control of pharyngeal dilator muscles due to neuropathy may be involved [8]. Nocturnal breathing abnormalities, such as snoring, choking, and, in severe cases, apnea/hypopnea events, occur in 25 to 35% of patients with hypothyroidism [8, 18]. Thyroid dysfunction has been shown to be a cause of OSA, but also contributes indirectly to OSA through its association with the metabolic syndrome (with obesity as a clinical sign), cardiovascular, and neuromuscular problems.

The evidence for SCH being linked to OSA is less clear, perhaps due to the absence of the severe impact that has been described in patients with OH [8, 9, 18]. Despite the absence of clinically obvious signs and symptoms, SCH has been associated with a higher prevalence of atherosclerosis, higher lipid profiles, and insulin resistance [20].

Differences between studies in the prevalence of OSA in patients with hypothyroidism may be explained, in part, by differences in whether or not the presence of goiter was taken into account. It is known that large goiters may also contribute to pharynx occlusion and OSA, independently of thyroid dysfunction [18, 21]. In our study, we did not perform echographies to search for the presence of goiter. The pathogenic relationship between large goiters and OSA may be attributed to increased edema with reduced patency of the upper airways, as a result of decreased venous return from the head and neck. Moreover, tracheal displacement may also

Table 1 Demographic characteristics and thyroid function as continuous data in all patients, according to OSA severity

Parameters (continuous) median [min–max] or mean ± SD	All patients $n = 280$ (100%)	OSA-moderate AHI < 30 $n = 76$ (27%)	OSA-severe AHI ≥ 30 $n = 204$ (73%)	p value
AHI (n)	*49.0 ± 25.4*	*22.8 ± 3.2*	*58.8 ± 23.1*	*< 0.001*
Age (years)	56.4 ± 12.7	56.7 ± 10.1	56.3 ± 13.5	0.858
BMI (kg/m^2)	32.8 ± 6.7	31.1 ± 4.8	33.4 ± 7.2	*0.009*
All serum TSH levels	1.8 [1.2–2.8]	2.2 [1.2–2.9]	1.8 [1.2–2.7]	0.285
TSH (mIU/L)*	1.8 [1.3–2.7]	2.1 [1.2–2.8]	1.7 [1.3–2.6]	0.378
All FT4 levels (pmol/L)	15.5 ± 2.5	15.7 ± 2.7	15.5 ± 2.4	0.470
FT4 (pmol/L)*	15.3 ± 2.3	15.3 ± 2.3	15.3 ± 2.3	0.981

Significant values are shown in italic

BMI, body mass index; *AHI*, apnea–hypopnea index; *FT4*, free T4

*After exclusion of patients treated with thyroid hormone supplements ($n = 25$)

interfere with the upper airway stiffening reflex which normally occurs during inspiration. A large goiter may itself create a mass loading effect on the airways, which is further compounded by reduced activity of the pharyngeal dilator muscles [22].

In this study, the severity of OSA was not associated with that of thyroid function (TSH or FT4) but with BMI levels that were the highest in the group with severe OSA, as previously well described [4, 5]. The correlation between thyroid function and obesity is well known but remains complex. Obese patients have higher mean serum levels of TSH and a higher risk of TAI [23]. Obesity is known to be associated with higher serum TSH levels, probably mediated via a leptin pathway leading to more TAI. Furthermore, increased deiodinase activity has been hypothesized to lead to high conversion rates of T4 to T3 as a compensatory mechanism for fat accumulation to improve energy expenditure [24]. In our study, we did not measure thyroid antibodies for the presence of TAI, and, thus, were not able to evaluate this aspect of the relationship between obesity and thyroid dysfunction.

The prevalence of SCH in patients with OSA has been investigated in a number of studies [18]. The prevalence of

Table 2 The prevalence of altered demographic characteristics and thyroid disorders as categorical data in all patients, according to OSA severity

Parameters (categoric), n (%)	All patients $n = 280$ (100%)	OSA-moderate AHI < 30 $n = 76$ (27%)	OSA-severe AHI ≥ 30 $n = 204$ (73%)	p value
Age ≥ 60 years	120 (43%)	27 (36%)	93 (46%)	0.130
Gender (male/female)	194/86 (70/30%)	43/33 (57/43%)	151/53 (74/26%)	*0.005*
Smokers	112 (40%)	19 (25%)	93 (46%)	*0.002*
HTA	147 (53%)	36 (47%)	111 (54%)	0.294
Obesity (BMI ≥ 30 kg/m^2)	192 (69%)	49 (65%)	143 (70%)	0.367
Newly diagnosed SCH (TSH > 4.2 mIU/L)**	18 (7.0%)	4 (6.0%)	14 (7.4%)	0.685
Newly diagnosed OH (TSH > 4.2 mIU/L, FT4 < 12 pmol/L)**	3 (1.2%)	0 (0%)	3 (1.6%)	0.298
Newly diagnosed SCH + OH**	21 (8.2%)	4 (6.0%)	17 (9.0%)	0.450
All SCH (TSH > 4.2 mIU/L)	21 (7.5%)	6 (7.9%)	15 (7.3%)	0.878
All OH (TSH > 4.2 mIU/L, FT4 < 12 pmol/L)	4 (1.4%)	0 (0%)	4 (2.0%)	0.219
All SCH + OH	25 (8.9%)	6 (7.9%)	19 (9.3%)	0.711
Patients under LT4	25 (8.9%)	9 (11.8%)	16 (7.8%)	0.297
Any kind of thyroid problem	46 (16.4%)	13 (17.1%)	33 (16.2%)	0.852

Significant values are shown in italic

BMI, body mass index; *AHI*, apnea–hypopnea index; *HTA*, hypertension; *SCH*, subclinical hypothyroidism; *OH*, overt hypothyroidism; *LT4*, thyroid hormone supplements

**After exclusion of patients treated with thyroid hormone supplements ($n = 25$)

Table 3 Spearman's ρ coefficients (p value) of the correlations between demographic characteristics, thyroid function parameters, and the apnea–hypopnea index

rho/p	AHI		Smoking		HTA (mmHg)		BMI (kg/m^2)		TSH (mIU/L)		FT4 (pmol/L)	
Age (years)	− 0.103	0.098	0.071	0.259	0.302	8.426	− 0.218	4E–04	− 0.04	0.538	− 0.05	0.431
AHI			0.052	0.405	0.071	0.257	0.347	1.152	0.065	0.297	− 0.06	0.369
Smoking					− 0.022	0.725	− 0.08	0.203	0.095	0.133	− 0.04	0.542
HTA (mmHg)							0.125	*0.044*	− 0.01	0.901	0.061	0.324
BMI (kg/m^2)									0.123	*0.049*	− 0	0.954
TSH (mIU/L)											− 0.19	*0.002*

Significant values are shown in italic

BMI, body mass index; *HTA*, hypertension; *OSA*, obstructive sleep apnea; *FT4*, free T4

newly diagnosed patients with OH varies between 0.4% and 1.9% [13, 14, 25], and between 0.6% and 11.5% for SCH [13, 14, 25]. Differences in prevalence values may be explained by the fact that, in older studies, less sensitive assays for serum TSH were used. Also, some studies were retrospective while others were prospective.

Some studies have evaluated the prevalence of hypothyroidism in OSA patients compared to that of non-OSA and age-, gender-, and BMI-matched controls. In a study by Winkelman et al. [25], the rate of OH was 1.5% in OSA patients and 0.7% in controls. In studies by Kapur et al. [26] and Miller et al. [27], the prevalence of hypothyroidism was similar in OSA patients and in the general population. However, in two other studies, the prevalence of SCH was higher in patients with OSA compared with that in controls. In that by Resta et al. [28], it was 11.5% versus 1% in a group of 200 patients referred to the obesity outpatient clinic, and in the study by Bahammam et al. [13], it was 11.1% versus 4% in non-OSA patients.

In our study, the prevalence of patients with newly diagnosed OH was 1.2% and the prevalence of SCH was 7%, figures in line with those in the literature. However, when we considered patients with known SCH, and those already treated with LT4 (f.i., post-thyroidectomy), the prevalence of any kind of thyroid disorder was as high as 16.4%. We did not include a control population for comparison of the prevalence of SCH and the prevalence for the Belgian population because for this population, age, gender, and BMI are unknown. However, the prevalence of thyroid disorders in the general Spanish population in different age groups in men and women has been recently published [29]. The global prevalence of total hypothyroidism (including OH, SCH, and LT4-treated patients) was 9.1%. As Spain is an area with a comparable iodine intake to Belgium, we can assume similar findings in our country, lower than the prevalence observed in the present study. Furthermore, we considered the possibility that a prevalence of 16.4% may be remarkably high since our study population consisted mainly of men. However, in the general population, it is known that the prevalence of SCH is at least twice as high in women compared with men [7].

The debate regarding whether patients with OSA should be screened systematically for the presence of thyroid dysfunction is ongoing. Discussion of factors related to the current definition of thyroid screening can provide insight into why this is still a controversial topic. The prevalence of OSA is high and increasing over time, with moderate-to-severe OSA occurring in 13% of men and 6% of women [4]. In patients with hypothyroidism, the prevalence of OSA has been reported to be 30% or higher [8]. However, the prevalence rates of OH and SCH in patients with OSA are estimated to be about 1% and 10% [18]. Thyroid hormone treatment (LT4) is a well-known, well-tolerated, and inexpensive treatment. The diagnosis of SCH is simple and consists of measurement of TSH and FT4. This test is accepted for the general population, and, thus, also for patients with OSA. Before patients are overtly hypothyroid and in the SCH stage, they are often asymptomatic. There is general consensus that patients with OH need to be treated with LT4 [7], but for patients with SCH, treatment is proposed according to risk stratification [30]. Screening for thyroid function has been estimated to be cost-effective in a setting of pregnancy, even if only overt disease is considered [31]. However, for the general population, the Preventive Services Task Force concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening for thyroid dysfunction in non-pregnant, asymptomatic adults [32].

In OSA patients suffering from OH, interventional studies have demonstrated a significant reduction in apnea periods, oxygen desaturation events, snoring, and choking with LT4 treatment [8, 18]. By contrast, when patients are obese, cure rates for OSA may be less impressive. The evidence for SCH being linked with OSAS is less clear.

Some limitations of our study were the absence of information on the presence of goiters, the fact that we did not check for thyroid autoimmunity, and the lack of data on the duration of existing SCH. We included only patients with moderate and severe OSA, but did not have an age-, sex-, and BMI-matched non-OSA healthy control group.

Altogether, in our OSA patients, mostly male and referred to our sleep unit for CPAP, we observed a high prevalence of thyroid problems compared with that commonly reported in age- and gender-matched subjects. However, our results need to be interpreted with caution since no age- and BMI-matched controls without OSA were investigated. Amelioration of OSA has been described in patients treated with LT4, independently from that of weight loss. Further research is needed to evaluate the relationship between thyroid disease and OSA, including measurement of thyroid antibodies, and analysis of the role of other factors such as obesity, gender, age, or goiters, for example. Additional information will assist in identifying suitable candidates for screening of thyroid disease. Nevertheless, our findings suggest that the prevalence of thyroid disorders is greater in the OSA population than that in the general population, in particular in patients with higher BMI.

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Author contributions K. Poppe and M. Bruyneel collected the data, performed data analyses, and prepared the manuscript. F. Veltri performed data analyses and prepared the manuscript.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the Saint-Pierre University Hospital Ethics Committee (AK/16-01-18/4613).

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

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