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BASIC SCIENCE • SHORT COMMUNICATION

Lack of associations between thyroid function and obstructive sleep apnea severity in adults with prediabetes and diabetes mellitus

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Abstract

Purpose Hypothyroidism is associated with a high frequency of obstructive sleep apnea (OSA). However, the prevalence of OSA in hypothyroid patients is not different from the general population in many reports. The importance of thyroid function screening in sleep-disordered breathing is still controversial. This study aimed to explore the association between thyroid dysfunction and OSA in the adults with prediabetes or diabetes mellitus type 2, who have very high prevalence of OSA.

Methods OSA was assessed using an in-home monitoring device, WatchPAT200. OSA severity was measured using apnea-hypopnea index (AHI), oxygen desaturation index (ODI), minimum oxygen saturation (minO2), and time spent under oxygen saturation < 90% (T90). Patients with pre-existing thyroid dysfunction were excluded.

Results Participants included 70 men and 118 women with mean age 52.8 ± 10.9 years and body mass index 28.2 ± 4.9 kg/m^2. One hundred forty participants (75%) had OSA, with a median AHI of 10.1 (interquartile range 4.8, 18.3). The percentage of positive thyroid autoantibody (thyroperoxidase and thyroglobulin antibody) was similar among the subjects with and without OSA. There was no correlation between the levels of thyroid function (TSH, FT3, FT4, TSH/FT3, and TSH/FT4 ratio) and the severity indices of OSA (AHI, ODI, minO2, and T90).

Conclusions These data do not support universal screening for thyroid dysfunction in OSA patients with diabetes or prediabetes.

Keywords Hypothyroidism · Polysomnography · Sleep apnea syndromes · Thyrotropin · Thyroxine · Triiodothyronine

Introduction

Hypothyroidism and obstructive sleep apnea (OSA) are both common in the general population and share several clinical presentations, including fatigue, lethargy, sleepiness, memory loss, and impaired concentration [1, 2]. A high prevalence of OSA up to 30% has been reported in patients with overt hypothyroidism [3]. However, hypothyroidism occurs only in a small number of cases with OSA, and several authors found insufficient evidence to recommend for universal thyroid function screening in OSA patients [4–8]. To date, there are no recommendations to routinely screen thyroid function in OSA patients. OSA is a novel risk factor for type 2 diabetes mellitus (T2DM), and is very common in patients with T2DM [9]. We aimed to determine the prevalence of thyroid dysfunction in OSA patients with T2DM and prediabetes, who are at very high risk for sleep apnea. The associations

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between thyroid function tests/thyroid autoantibodies and OSA were also explored.

Methods

This cross-sectional study, conducted between 2014 and 2016, enrolled the adults aged > 18 years with a documented clinical diagnosis T2DM or prediabetes (fasting plasma glucose 100–125 mg/dL and hemoglobin A1c < 6.5%) who were evaluated for OSA by using WatchPAT200 (Itamar Medical, Israel), an FDA-approved overnight in-home monitoring device. OSA was diagnosed when apnea hypopnea index (AHI) was ≥ 5, using the manufacturer's automated software. Other sleep parameters included oxygen desaturation index (ODI), minimum O2 (the lowest oxygen saturation value over the recording period), and T90 (percentage of total sleep time in which the oxygen saturation remains < 90%). Written informed consent was obtained from all participants. The study was approved by the Ethics Committee. We excluded patients with diagnosed OSA, lower airway disease, heart/renal/hepatic failure, history of stroke, pregnancy, use of medications that might affect respiratory function, and patients who had implanted permanent pacemaker. Baseline characteristics (age, sex, body weight, height, neck, waist, and hip circumference) were recorded. Laboratory tests included fasting plasma glucose, hemoglobin A1c, FT3 (free triiodothyronine), FT4 (free thyroxine), thyroid-stimulating hormone (TSH), thyroperoxidase antibody (TPOAb), and thyroglobulin antibody (TgAb). Thyroid function and thyroid autoantibodies were measured by electrochemiluminescence immunoassay on a Cobas e411 analyzer (Roche Diagnostics, Germany). The normal ranges of serum TSH, FT4, TPOAb, and TgAb are 0.27–4.2 mIU/L, 0.93–1.71 ng/dL, 0–34 IU/mL, and 0–115 IU/mL, respectively. Patients with pre-existing thyroid dysfunction were excluded.

Statistical analysis was performed using STATA (StataCorp, USA). Data are shown as mean ± standard deviation and median (interquartile range) as appropriate. To explore variables, the associations between independent factors and OSA severity, univariate analysis was performed. Subsequently, variables with p values < 0.1 were evaluated using a multivariate analysis. P values < 0.05 were considered significant.

Results

A total of 188 participants (70 males and 118 females) with mean age 52.8 ± 10.9 years and body mass index (BMI) 28.2 ± 4.9 kg/m^2 were included. Of these, 140 patients (75%) had OSA defined by AHI ≥ 5 with a median AHI of 10.1 (interquartile range 4.8, 18.3). None had overt thyroid dysfunction. Fifteen patients (8%) had subclinical hypothyroidism defined by elevated TSH and normal FT4. Two patients (1%) had subclinical hyperthyroidism defined by suppressed TSH and normal FT4. There were no cases with low FT3 level. The prevalence of thyroid dysfunction was 6.8% and 14.6% in OSA (N = 140) and non-OSA (N = 48) participants, respectively.

In the group of subclinical hypothyroidism, 4 subjects were diagnosed as mild OSA (AHI ≥ 5 but < 15), 3 as moderate OSA (15 ≤ AHI < 30), and 3 as severe OSA (AHI ≥ 30). The prevalence of OSA was 66.7% and 75.9% in subclinical hypothyroid and euthyroid participants (normal TSH and FT4), respectively. Subjects with subclinical hypothyroidism had no significance differences in AHI, minO2, ODI, and T90, compared with euthyroid subjects. No significant differences in FT3, FT4, TSH, TPOAb, and TgAb were demonstrated among participants with different severities of sleep apnea (Table 1). The ratios of TSH/FT3 and TSH/FT4 were also not correlated with OSA severities (data not shown).

The univariate analysis of the multiple factors versus the severity indices of OSA is presented in Table 2. There was no collinearity among the variables. Thyroid function had no significant correlation with OSA severity indices. The multivariate analysis using stepwise regression was performed and the results were summarized in Table 3. Waist-height ratio showed the most significant correlation with AHI, minO2, ODI, and T90.

Discussion

This study demonstrated the lack of association of thyroid function and thyroid autoantibodies with the severity indices of OSA in a high-risk population for OSA, e.g., patients with T2DM or prediabetes. The prevalence of thyroid dysfunction in OSA patients was similar to those of the general population [10]. The prevalence of OSA was not higher in subjects with subclinical hypothyroidism compared with euthyroid group. Our results are consistent with several studies that showed no significant differences in the levels of thyroid function among patients with different severities of sleep apnea [4, 11–13]. In our study, FT3 levels and the prevalence of Hashimoto's thyroiditis were not correlated with severities of OSA, contrary to previous reports [13, 14]. Waist-height ratio highly correlated with the severity of OSA. Our data do not support thyroid function screening in patients with OSA.

Hypothyroidism plays a role in pathogenesis of sleep apnea via multifactorial mechanisms including decreased ventilatory drive, obesity, myopathy, and upper airway narrowing due to myxedamatous change [15]. The key contributor to OSA in hypothyroidism is from mucopolysaccharide deposition of the upper airway, which may

Table 1 Baseline characteristics

	No OSA ($N = 48$)	Mild OSA ($N = 74$)	Moderate OSA ($N = 43$)	Severe OSA ($N = 23$)	*P* value
Female, no.(%)	36 (75%)	48 (64%)	25 (58%)	9 (39%)	0.028
Age, years	49.5 ± 11	53.8 ± 10.6	54.8 ± 11	52.4 ± 10.4	NS
BW, kg	65.9 ± 13	71.5 ± 13.4	71 ± 13.5	88.1 ± 15.9	< 0.001
BMI, kg/m^2	26.0 ± 4.4	28.3 ± 4.6	27.8 ± 4.1	33.0 ± 4.8	< 0.001
Waist-hip ratio	0.90 ± 0.07	0.93 ± 0.07	0.95 ± 0.07	0.99 ± 0.06	< 0.001
Waist-height ratio	0.56 ± 0.07	0.59 ± 0.01	0.60 ± 0.06	0.66 ± 0.63	< 0.001
Neck circumference, cm	35.2 ± 3.4	36.5 ± 3.7	37.1 ± 3.5	40.1 ± 3.9	< 0.001
HbA1c, %	7.2 ± 1.9	7.1 ± 1.5	7.2 ± 1.5	7.8 ± 1.5	NS
FT3, pg/mL	3.75 ± 0.72	3.64 ± 0.46	3.67 ± 0.39	3.79 ± 0.61	NS
FT4, ng/dL	1.34 ± 0.19	1.35 ± 0.20	1.31 ± 0.19	1.40 ± 0.16	NS
TSH*, mIU/L	1.97 (0.04–9.92)	2.09 (0.04–6.24)	2.24 (0.69–7.01)	1.84 (0.45–8.71)	NS
TPOAb+, TgAb+	4 (8%)	6 (8%)	0 (0%)	0 (0%)	NS
TPOAb+, TgAb-	3 (6%)	6 (8%)	0 (0%)	1 (4%)	NS
TPOAb-, TgAb+	3 (6%)	5 (7%)	3 (7%)	2 (9%)	NS

*Data presented as median (interquartile range); severity of obstructive sleep apnea (OSA) is classified as follows: no OSA, AHI < 5; mild OSA, AHI 5 to < 15; moderate OSA, AHI 15 to < 30; severe OSA, AHI ≥ 30 events per hour

BMI, body mass index; *BW*, body weight; *FT3*, free triiodothyroxine; *FT4*, free thyroxine; *HbA1c*, hemoglobin A1c; *NS*, non-significance; *OSA*, obstructive sleep apnea; *TgAb*, thyroglobulin antibody; *TPOAb*, thyroperoxidase antibody; *TSH*, thyroid-stimulating hormone

predispose to obstruction during sleep either directly by soft-tissue thickening or elevation of pharyngeal collapsibility [3]. Overt hypothyroidism appears to be linked to OSA, with a significant improvement by levothyroxine replacement [3]. While universal screening for TSH may theoretically be beneficial to detect undiagnosed hypothyroidism in the patients with OSA, there are currently no data to support such as approach. In addition, in absence of overt symptoms, levothyroxine therapy results in little or no beneficial effects on sleep apnea in patients with subclinical hypothyroidism [16, 17]. However, thyroid function should be evaluated in the patients at high risk, e.g., history of thyroid dysfunction, presence of a goiter, autoimmune disorders, morbid obesity, use of amiodarone, lithium, and residing in area of moderate to severe iodine deficiency [18]. Currently, no medical organization recommends routine screening for thyroid dysfunction in those with OSA. The decision regarding screening for hypothyroidism must be considered when evidence from large population study becomes available.

Table 2 Univariate analysis of multiple variables versus the severity indices of obstructive sleep apnea

	AHI	*P* value	MinO2	*P* value	ODI	*P* value	T90	*P* value
Age	0.11	NS	0.07	NS	0.05	NS	− 0.01	NS
FT3	− 0.02	NS	− 0.75	NS	0.58	NS	0.23	NS
FT4	4.50	NS	− 2.26	NS	0.39	NS	1.17	NS
TSH	0.14	NS	− 0.34	NS	0.04	NS	− 0.11	NS
Female	− 5.66	0.005	2.73	0.043	− 4.80	0.004	− 1.32	0.024
BW	0.35	< 0.001	− 0.23	< 0.001	0.28	< 0.001	0.10	< 0.001
BMI	1.08	< 0.001	− 0.76	< 0.001	0.86	< 0.001	0.28	< 0.001
Waist-hip ratio	58.19	< 0.001	− 34.46	< 0.001	45.64	< 0.001	11.55	0.003
Waist-height ratio	56.79	< 0.001	− 36.06	< 0.001	45.56	< 0.001	13.82	< 0.001
Neck circumference	1.16	< 0.001	− 0.87	< 0.001	0.96	< 0.001	0.277	< 0.001
HbA1c	1.20	0.048	− 1.23	0.002	1.01	0.044	0.25	NS

Each digit expresses correlation coefficient

AHI, apnea-hypopnea index; *BMI*, body mass index; *BW*, body weight; *FT3*, free triiodothyroxine; *FT4*, free thyroxine; *HbA1c*, hemoglobin A1c; *MinO2*, minimum oxygen saturation; *NS*, non-significance; *ODI*, oxygen desaturation index; *T90*, time spent under oxygen saturation < 90%; *TSH*, thyroid-stimulating hormone

Table 3 Stepwise regression analysis of each severity indices of obstructive sleep apnea

AHI	Beta	*P* value	95%CI	
Waist-height ratio	81.56	< 0.001	57.79	105.34
Female	− 6.80	< 0.001	− 10.37	− 3.22
Age	0.19	0.021	0.03	0.35
MinO2	Beta	*P* value	95%CI	
Waist-height ratio	− 35.77	< 0.001	− 53.58	− 17.96
Neck circumference	− 0.48	0.007	− 0.82	− 0.13
HbA1c	− 0.78	0.036	− 1.50	− 0.05
ODI	Beta	*P* value	95%CI	
Waist-height ratio	62.92	< 0.001	43.02	82.82
Female	− 5.37	0.001	− 8.36	− 12.38
T90	Beta	*P* value	95%CI	
Waist-height ratio	9.32	< 0.001	− 13.42	− 4.86
BW	0.07	0.003	0.02	0.11

AHI, apnea-hypopnea index; *BW*, body weight; *CI*, confidence interval; *HbA1c*, hemoglobin A1c; *MinO2*, minimum oxygen saturation; *ODI*, oxygen desaturation index; *T90*, time spent under oxygen saturation < 90%

Strengths of this study are the complete investigations of FT3, FT4, TSH, and thyroid autoantibodies. However, a single measurement result of thyroid function does not completely rule out thyroid dysfunction. Isolated abnormal TSH concentrations can be transient without important consequences. OSA was not diagnosed by the gold standard polysomnography, which could be a limitation of the study. The device used also could not differentiate central apnea from OSA; however, we excluded patients at high risk for central apnea as outlined in the methods. This study was conducted in participants with impaired glucose metabolism that may limit generalization to a broader population. This weakness of the study is also a strength because we explored the associations in T2DM population that has a high prevalence of thyroid dysfunction [19]. Our results have broadened the understanding of the endocrine disorders related with OSA, in addition to acromegaly, male hypogonadism, and growth hormone deficiency [20].

In conclusion, current evidence does not support a routine screening for thyroid function in OSA patients in absence of obvious clinical features of hypothyroidism.

Author's contributions Study concept and design, manuscript drafting: CS, SP, OS, SR. Data collection: HN, NC, SS, TA, NS, AM, LC, SR. Data interpretation, critical revision of the manuscript, and final approval: all authors.

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Compliance with ethical standards

Competing interests HN received honoraria from Sanofi, Novo Nordisk, MSD, Takeda, Novartis, Amgen, and AstraZeneca. SR received a grant from MSD and honoraria from Sanofi, Medtronic, Novo Nordisk, and research equipment support from ResMed, Thailand. All other 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/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

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Comment

The factors contributing to Obstructive Sleep Apnea risk and the severity of its manifestation are numerous and interact in complex ways. We usually treat the symptoms of the disorder, without a clear idea of its underlying etiology. In some cases OSA is secondary to another disease state, which when treated can ameliorate OSA symptoms or facilitate treatment of OSA by customary means.

This paper investigates a potential connection between OSA and Hypothyroidism. The researchers chose a population, Diabetics and pre-diabetics, that is at high risk for OSA. DM2 is also thought to be a risk factor for hypothyroidism. The high prevalence of OSA in patients with hypothyroidism is understandable since weight gain and decreased respiratory drive among other symptoms of hypothyroidism predispose to OSA. On the other hand, it has not been reported that OSA might influence onset of hypothyroidism, but since hypothyroidism is treatable, it is reasonable to investigate this potential association as a means of informing clinical guidelines concerning screening for hypothyroidism in OSA patients.

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