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Screening TSH in Obstructive Sleep Apnea Syndrome: Null or Beneficial?

Tıkayıcı Uyku Apne Sendromunda TSH Taraması: Faydasız ya da Faydalı?

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Abstract

Objective: The link between obstructive sleep apnea syndrome (OSAS) and hypothyroidism, which is associated with mucopolysaccharide infiltration and swelling of the soft tissues of the upper airway, is known for years. However, reports regarding the frequency of hypothyroidism in OSAS, as well as the requirement of screening thyroid stimulating hormone (TSH), have inconsistent results. This study aims to reveal the actual frequency of hypothyroidism among individuals with complaints suggestive of OSAS and provide a rationale for whether or not to screen.

Materials and Methods: Two hundred eighty-two patients evaluated due to complaints suggesting OSAS and underwent overnight diagnostic polysomnography were retrospectively reviewed. Demographic, clinical, and polysomnographic parameters and serum TSH levels were analyzed and compared between OSAS patients and those with a normal apnea-hypopnea index (AHI). A multiple linear regression model was used to adjust for potential confounders. A two-tailed p-value of <0.05 was accepted as statistically significant.

Results: No patient from the entire study population was diagnosed with overt hypothyroidism. Pairwise comparisons between OSAS patients and non-OSAS controls revealed similar results in terms of TSH levels (1.62 mIU/L vs 1.44 mIU/L, p=0.258) and subclinical hypothyroidism frequency (3.2% vs 3.4%, p=0.934). There was no association between the TSH levels and AHI values.

Conclusion: According to these results, a TSH screen does not seem to be a mandatory part of routine workups in patients with sleep-disordered breathing symptoms for uncovering clinical hypothyroidism. Limiting TSH screening mainly to patients with marked symptoms regarding hypothyroidism would be appropriate in this population.

Keywords: Obstructive sleep apnea syndrome, clinical hypothyroidism, subclinical hypothyroidism, TSH

Öz

Amaç: Tıkayıcı uyku apne sendromu (TUAS) ve hipotiroidizm arasında yıllardan beri iyi tanımlanmış bir ilişki mevcuttur. Hipotiroidizmin üst solunum yollarını da içine alan yumuşak dokuda diffüz mukopolisakkarid birikimi üzerinden TUAS patofizyolojisine katkıda bulunduğu bilinmektedir. Bununla birlikte TUAS'de hipotiroidizmin sıklığı ve dolayısıyla da tiroid stimule edici hormon (TSH) taramasının gerekliliğini değerlendiren çalışmalarda çelişkili sonuçlar olduğu görülmektedir. Bu çalışmada amaç, TUAS şüphesiyle değerlendirilen hastalarda hipotiroidizmin gerçek sıklığını belirlemek ve bu popülasyonda TSH taramasının gerekli olup olmadığını ortaya koymaktır.

Gereç ve Yöntemler: TUAS şüphesi ile değerlendirilerek bir gecelik tanısal polisomnografiye tabi tutulan 282 hastanın kayıtları geriye dönük incelendi. Olguların klinik, demografik, polisomnografik bulguları ve TSH düzeyleri kaydedilerek OSAS saptanan ve saptanmayan grupta karşılaştırıldı. TSH düzeyleriyle ilişkisi olabilecek potansiyel değişkenler için çoklu hiyerarşik regresyon modeli uygulandı. P<0,05 istatistiksel olarak anlamlı kabul edildi.

Bulgular: Çalışma popülasyonundaki hiçbir olguda klinik hipotiroidizm saptanmadı. TUAS saptanan ve saptanmayan grupta TSH düzeyleri (1,62 mIU/L vs 1,44 mIU/L, p=0,258) ve subklinik hipotiroidizm oranlarının (%3,2 vs %3,4, p=0,934) benzer olduğu görüldü. TSH değerleri ile apne-hipopne indeksi arasında bir ilişki saptanmadı.

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Sonuç: Mevcut çalışmada elde edilen bulgular, uyku ilişkili solunum bozukluğu şüphesi ile değerlendirilen olgularda rutin TSH taramasının klinik hipotiroidizmi saptamak yönünden ek bir katkı sağlamadığını göstermektedir. Bu popülasyonda TSH taramasının, hipotiroidizmle ilişkili belirgin semptomlar tanımlayan olgularda tercih edilmesi uygun görünmektedir.

Anahtar Kelimeler: Tıkayıcı uyku apne sendromu, klinik hipotiroidizm, subklinik hipotiroidizm, TSH

Introduction

Obstructive sleep apnea syndrome (OSAS) is basically characterized by partial and/or complete obstructions of the upper airway - frequently in association with intermittent hypoxia and arousals- during sleep and often presented with the typical clinical triad of snoring, excessive daytime sleepiness and witnessed apnea. It is a prevalent disorder among public which results in a number of cardiovascular and metabolic consequences and the common comorbidities include hypertension, obesity/metabolic syndrome, diabetes mellitus, coronary artery disease, cardiac arrhythmias, cerebrovascular diseases, pulmonary hypertension, cor pulmonale and etc. (1,2). The estimated prevalence approximates 2-5% among women and 3-7% among men which necessitates early diagnosis and identification of the population at high risk for screening (3). Hypothyroidism, which is another common disorder with prevalence rates of 3.7-5%, is accounted as a predisposing factor for years because of its undesirable contributions to the collapsibility of upper airway (4,5). Nevertheless, studies evaluating the frequency of hypothyroidism in OSAS state conflicting results. Although average rates between 0.7-3.4% have been reported in large cohorts; some researchers described a frequency up to 11.5% among 78 obese/overweight individuals referred to a sleep clinic (6,7). Beyond that, the situation gets more complicated while talking about subclinical hypothyroidism (SH) which have prevalence rates of 4.3-5% approximately (8,9). Since relevant data regarding the predisposing role of SH in OSAS is divergent and the disorder represents an asymptomatic state as in the name; the need for screening or potential benefits of documentation are either not clear.

The objective of this retrospective study is to reveal the actual frequency of hypothyroidism among individuals with complaints suggestive of OSAS and provide a rationale for whether or not to screen.

Materials and Methods

Medical charts of patients who were evaluated with at least one of the complaints including snoring, excessive daytime sleepiness, and witnessed apnea, and who underwent overnight polysomnography in the Sleep Laboratory of a single center between July 2017 and February 2019 were retrospectively reviewed. Demographic parameters (age and sex), anthropometric measures [body mass index (BMI)], scores of the Epworth sleepiness scale (ESS), polysomnographic indices, and laboratory data regarding serum thyroid stimulating hormone (TSH) levels were recorded. This retrospective study was approved by the Ethics Committee of Aydın Adnan Menderes University (protocol no: 2019/50, date: 21.03.2019).

Patients with a diagnosis of overt hypothyroidism before admission [previous TSH levels of >10 mIU/L (10), and/or receiving levothyroxine -LT4- replacement therapy], patients that use any medication that may influence TSH levels like lithium, dopamine agonists, amiodarone, etc., and patients without available laboratory data were excluded.

Nox Medical Programme was used for polysomnographic data acquisition and analysis. The recordings included electrooculogram, six-channel electroencephalogram, electrocardiogram, chin and leg electromyogram, oronasal thermal and nasal airflow, pulse oximetry, thoracic and abdominal respiratory effort and body position. The polysomnographic data were scored manually following the rules of AASM 2014 v2.4 guidelines (11). The severity of OSA was graded depending on the apnea-hypopnea index (AHI). An AHI value between ≥5 and <15 events/hour was categorized as mild OSAS; while the values between ≥15 and <30 events/hour were categorized as moderate and ≥30 events/hour as severe OSAS (12). Individuals with an AHI value of <5 events/hour did serve as the non-OSAS control group.

During the initial visit to the outpatient clinic, a complete physical and neurological examination was performed in addition to respiratory function tests, and serum TSH levels were either measured on the same morning after an overnight fast via the automatic chemiluminescence method. Overt/clinical hypothyroidism was diagnosed in the case of a newly detected TSH level >10 mIU/L as mentioned above (10).

An elevated TSH level indicative of SH was defined as >4.0 mIU/L and <10 mIU/L for this study, since 90% of patients with SH are known to have TSH levels between 4 and 10 mIU/L (13,14), and the usual goal of replacement therapy with levothyroxine in overt hypothyroidism is to achieve a range between 0.4-4.0 mIU/L regarding optimal TSH values (5).

Statistical Analysis

IBM.SPSS.20 package program (SPSS, Inc., Chicago, Illinois) was used for statistical analysis. The Shapiro-Wilk test was performed to assess the normality of numeric data. Continuous variables were presented as mean ± standard deviation or median (minimum-maximum) according to the normality. Categorical variables were presented as percentages and analyzed by the chi-square test. For pairwise comparisons, Independent samples t or Mann-

Whitney U test was performed and when the number of groups is more than two, one-way ANOVA or Kruskal-Wallis variance analysis was used together with posthoc tests. A multiple linear regression model was used to adjust for potential confounders. A two-tailed p-value of <0.05 was accepted as statistically significant.

Results

Two hundred eighty-two patients were included in the study. Two hundred fifty-three patients with characteristic symptoms satisfied the diagnostic criteria for OSAS (AHI ≥5/hour), whereas the remaining 29 had normal AHI values (<5/hour) and served as the non-OSAS control group. The median TSH level in the non-OSAS control group was 1.44 mIU/L, whereas the corresponding value was 1.62 mIU/L in the OSAS group (p=0.258). Neither an individual out of the OSAS patient group nor non-OSAS controls had a current TSH value of >10mIU/L compatible with overt hypothyroidism.

12% of OSAS (n=30) patients were diagnosed with mild disease, while 27% (n=68) had moderate and 61% (n=155) had severe disease. Age, sex, ESS scores and TSH values were similar among three grades of disease regarding OSAS patients, however severe OSAS group had higher BMI values when compared to the patients with mild and moderate disease (p<0.001*). In a similar manner, both sleep and hypoxia related polysomnographic indices demonstrated significant difference against severe disease group (Table 1). No significant correlation was observed between AHI values and TSH levels among OSAS patients (r=0.045, p=0.477).

Pairwise comparisons between OSAS patients and non-OSAS controls revealed similar results in terms of male rate, ESS score and TSH levels (p>0.05). However median age was younger (43.5 yrs vs 52 yrs, p<0.001) and median BMI was lower among non-OSAS controls. (30,45 kg/m^2 vs 32 kg/m^2, p=0.012) (Table 2).

The frequency of SH was 3.2% among OSAS patients (n=8), whereas the relative rate was 3.4% for the non-OSAS control group (n=1) (p=0.931) (Figure 1).

A multiple stepwise regression analysis revealed that TSH level was significantly associated with age and BMI. However, a similar association was not true for AHI (Table 3).

Discussion

In the current study, our results demonstrated that screening a considerable number of individuals with complaints suggesting OSAS failed to detect any case of overt hypothyroidism. Besides, no difference was established between OSAS patients and non-OSAS controls in terms of TSH levels or rates of SH.

The link between hypothyroidism and OSA syndrome, which arises from the narrowing of the upper airway, has been identified clearly for years, and hypothyroidism seems to act through several mechanisms during this pivotal process. Mucopolysaccharide infiltration of anatomical

Table 1. Baseline characteristics and polysomnographic findings in OSAS patients

	Mild OSAS (n=30)	Moderate OSAS (n=68)	Severe OSAS (n=155)	p-value
Male rate (%)	56.7% (n=17)	73.5% (n=50)	74.2% (n=115)	0.139
Age [yrs. (range)]	52.5 (18-76)	46 (22-80)	53 (24-81)	0.173
BMI [kg/m^2 range)]	28.85 (21.4-37.3)	30.05 (20.8-45.7)	34 (19-68.7)*	<0.001*
ESS	4 (0-13)	4 (0-21)	6 (0-19)	0.116
TSH levels (mIU/L)	1.27 (0.64-6.07)	1.81 (0.23-3.53)	1.88 (0.03-6.89)	0.537
Polysomnography - sleep parameters				
TST (min)	375 (281.5-446)	368 (177.5-477.1)	332 (97.5-448)*	0.001*
Sleep eff. (%)	83.3 (59.9-95.7)	80.7 (41.3-95)	73.4 (26.8-95)*	<0.001*
N3 sleep (%)	16.8 (6.3-31.6)	17.6 (1.1-41.5)	8.3 (0-37.1)*	<0.001*
Polysomnography - respiratory parameters				
AHI (events/hour)	9.55 (5.3-14.4)	21.48 (15.2-29.8)	59.2 (30.1-11.64)	<0.001*
ODI	9.1 (0.8-44.3)	21.95 (5.3-47.3)	66.6 (17.6-141.5)*	<0.001*
spO_2<90% dur (%)	1.45 (0-41.6)	1.45 (0-83.5)	16.7 (0-100)*	<0.001*
Average spO_2	93.15 (89.5-96.6)	93.1 (87.9-96.7)	91.5 (61.5-96.1)*	<0.001*

OSAS: Obstructive sleep apnea syndrome, BMI: Body mass index, ESS: Eppworth Sleepiness Scale, TSH: Thyroid stimulating hormone, TST: Total sleep time, Sleep eff: Sleep efficiency, AHI: Apnea-hypopnea index, ODI: Oxygen desaturation index, spO_2<90% dur: Time spent <90% spO_2. P<0.05 denotes statistical significance

structures throughout the upper airway and swelling of these soft tissues, as a result, presence of goiter, impaired function of upper airway dilator muscle due to neuropathy and increased weight as a consequence of expansion in water compartment, or obesity itself could all contribute to narrowing of the upper airway, which becomes more evident during sleep (15). Also, severe hypothyroidism is known to be associated with a negative influence on hypoxic and hypercapnic responses of chemosensors, thus respiratory drive. The diaphragm was demonstrated to be weak in hypothyroid patients which give rise to decreased lung volumes and this also deteriorates the clinical picture of sleep apnea (15,16). Replacement therapy with LT4 has been demonstrated to reverse sleep-disordered breathing in some studies; in some of which the selection bias could not be completely excluded (16-18). However, management of overt hypothyroidism with proper replacement therapy in the presence of comorbid OSAS seems essential. On the other side, the co-existence of these two disorders in an individual appears to be incidental since both have a high prevalence among the general population (16). In a study cohort of 418 individuals, Bahammam et al. (19) revealed no difference regarding clinical hypothyroidism between OSA patients and non-OSAS controls (0.4% vs 1.4%). Among 203 patients, who underwent polysomnography due to sleep-disordered breathing symptoms, Ozcan et al. (20) defined an overt hypothyroidism rate of 1.9%, which was not higher than the general population. Mete et al. (21) detected clinical hypothyroidism in 4% of their OSAS patients, whereas the related rate was 6.2% for non-OSAS controls.

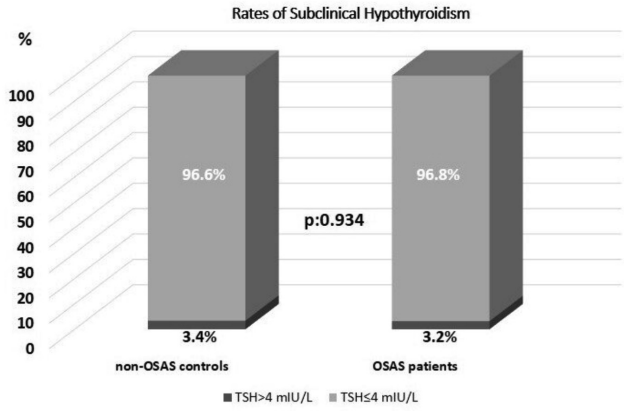

Figure 1. Rates of subclinical hypothyroidism among OSAS patients and non-OSAS controls

OSAS: Obstructive sleep apnea syndrome, TSH: Thyroid stimulating hormone

In the context of SH, the results are contradictory though. Despite the proportion of cases with SH being 11.1% and 10.8% respectively for the first two of the abovementioned studies (19,20); Mete et al. (21) reported a 4.7% rate of SH for OSAS, whereas the corresponding value was 6.2% for

Table 2. Baseline characteristics of study population

	Non-OSAS controls (n=29)	OSAS patients (n=253)	p-value
Male rate (%)	55.2%	71.9%	0.062
Age [yrs. (range)]	43 (18-61)	52 (18-81)*	<0.001*
BMI [kg/m^2 (range)]	30.4 (18.9-36.1)	32 (19-68.7)*	0.012*
ESS	6 (1-17)	5 (0-21)	0.534
TSH levels (mIU/L)	1.44 (0.26-4.32)	1.62 (0.03-6.89)	0.258

BMI: Body mass index, ESS: Eppworth sleepiness scale, OSAS: Obstructive sleep apnea syndrome, TSH: Thyroid stimulating hormone. P<0.05 denotes statistical significance

Table 3. Coefficients of stepwise multiple linear regression analysis for TSH

	TSH											
Variables	Model 1				Model 2				Model 3			
	B	Sh	β	t	B	Sh	β	t	B	Sh	β	t
Age	-0.012	0.005	-0.152	-2.556*	-0.012	0.005	-0.152	-2.556*	-0.013	0.005	-0.158	-2.643**
BMI					0.022	0.009	0.140	2.379*	0.020	0.011	0.123	1.860
AHI									0.001	0.003	0.038	0.566
Adjusted R2	0.019				0.036				0.033			
F change	6.535*				5.662*				0.320			
F	6.535*				6.153**				4.199**			

TSH: Thyroid stimulating hormone, BMI: Body mass index, AHI: Apnea-hypopnea index
*Correlation is significant at the 0.05 level. **Correlation is significant at the 0.01 level (two-tailed)

non-OSAS controls in their cohort. Similarly, Kapur et al. (22) identified SH in only 4 out of their 284 patients (1.4%), which was not higher than the general population either.

In our cohort, none of the patients from either the OSAS or non-OSAS group was newly diagnosed with clinical hypothyroidism, and SH rates were similar between the two. SH is known to attribute to an abnormal laboratory finding in the absence of clinical symptoms. Although overt hypothyroidism has been linked to OSA pathophysiology through several pathways, accumulating data has not verified the majority of these interactions for SH. Moreover, LT4 replacement did not demonstrate any improvement regarding respiratory disturbance in OSAS patients with SH (14). Hence there is not enough evidence yet, for screening SH in an asymptomatic population.

Our results support the restriction of TSH screening mainly to patients with marked symptoms. Since the rate of SH rather than overt form is evident in epidemiologic data regarding OSAS, and patients with SH have been demonstrated not to benefit from LT4 treatment in terms of respiratory disturbance, screening TSH does not seem to be beneficial in patients with a suspected diagnosis of OSAS.

Study Limitations

Our study has some limitations due to its retrospective design and absence of follow-up data. The magnitude of patients and controls, as well as the number of patients in each group regarding disease severity, was different in the current study, which was in favor of the severe group. Although this can be considered a disadvantage, it is also compatible with the accumulating epidemiological data in the literature. In comparison to mild and moderate patients, severe OSA patients comprise the majority of cases examined with sleep-disordered breathing complaints in sleep clinics (23,24). Also, the accepted cut-off value of TSH in our study might result in the underdiagnosis of some SH cases since recent reports by some experts suggest more strict upper limits for TSH (2.5-3 mIU/L) (25).

Conclusion

However, lowering the TSH cut-off would probably not influence the current results, as the subsequent increase in diagnosis would mainly include SH cases rather than overt hypothyroid ones, who already would not undergo treatment with LT4 replacement that rationalize TSH screening.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Ethics Committee of Aydın Adnan Menderes University (protocol no: 2019/50, date: 21.03.2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: U.O.A., Concept: U.O.A., A.A., Design: U.O.A., A.A., Data Collection or Processing: U.O.A., A.A., Analysis or Interpretation: U.O.A., A.A., Literature Search: U.O.A., A.A., Writing: U.O.A.

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