Long Oxygen Desaturation Time is a Risk Factor for Metabolic Syndrome

Uzun Oksijen Desaturasyon Süresi Metabolik Sendrom İçin Risk Faktörüdür

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Abstract

Objective: To assess metabolic syndrome (MS) prevalence in patients with obstructive sleep apnea syndrome (OSAS) and to evaluate the relationship between sleep parameters and MS incidence.

Materials and Methods: Included in this study were 101 patients with complaints of snoring, witnessed apnea, excessive daytime sleepiness, and no prior OSAS diagnosis. An apnea-hypopnea index (AHI) score ≥5 was required for the diagnosis of OSAS. The patient group included 80 cases, and the control group (AHI <5) included 21 cases. MS diagnosis was based on the National Cholesterol Education Program Adult Treatment Panel III.

Results: MS was diagnosed in 33.3% of controls (7/21) and in 66.3% of OSAS patients (53/80) (p=0.006). The MS frequency was 51.7% (15/29) in mild OSAS (AHI 5-14), 77.8% (14/18) in moderate OSAS (AHI 15-29.9), and 72.7% (24/33) in severe OSAS (AHI ≥30). In patients with oxygen desaturation time (ODT) <5.75 minutes, the MS frequency was 38.9%, while it was 74.2% in patients with ODT ≥5.75 minutes (p=0.005). In the logistic regression analysis with multiple variables (including AHI ≥5, body mass index [BMI] ≥27 kg/m^2, age and ODT ≥5.75), it was determined that ODT, age and BMI increase the risk of MS independent of other risk factors.

Conclusions: We found that ODT, age and BMI, which are independent of other risk factors, are determinants of MS in patients with OSAS. Additionally, the time of hypoxia, which is independent of AHI, also increases the risk of MS. *Turk Jem 2008; 12: 63-7*

Key words: Obstructive sleep apnea syndrome, metabolic syndrome, oxygen desaturation time

Özet

Amaç: Obstrüktif uyku apne sendromlu (OUAS) hastalarda metabolik sendrom (MS) prevalansını saptamak ve uyku parametreleri ile metabolik sendrom sıklığı arasındaki ilişkiyi değerlendirmek.

Gereç ve Yöntemler: Çalışmaya göğüs hastalıkları uyku laboratuvarına horlama, tanıklı apne, gündüz aşırı uyku hali yakınmaları ile başvuran daha öncesinde OUAS tanısı olmayan 101 hasta çalışmaya alındı. OUAS tanısı Apne hipopne index (AHI) ≥5 olması ile konuldu. AHI <5 olana hastalar kontrol grubu olarak seçildi. Metabolik sendrom tanısı NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III Report) kriterlerine göre konuldu.

Bulgular: Kontrol grubunda %33.3 (n=7/21), hasta grubunda ise %66.3(n=53/80) vakaya metabolik sendrom tanısı konuldu(p=0.006). MS sıklıkları AHI=5-14.9 olanlarda %51.7 (15/29), AHI=15-29.9 olanlarda %77.8 (14/18), AHI ≥30 72.7 (24/33)olanlarda saptandı. Oksijen desaturasyon süresi (ODT) 5.75 dakikadan uzun olanlarda metabolik sendrom sıklığı %74.2 (51/80) iken, 5.75 dakikadan kısa olanlarda MS sıklığı %38.9 (8/21) saptandı (p=0.005). AHI >15, yaş, BMI >27 kg/m^2 ve ODT >5.75 dakika ktiterleri dahil edilerek yapılan lojistik regresyon analizinde yaş, BMI ve ODT'nin diğer risk faktörlerinden bağımsız olarak metabolik sendrom olma riskini artırdığını saptadık.

Sonuç: OSAS'lı hastalarda oksijen desaturasyon süresi ve BMI nin diğer risk faktörlerinden bağımsız MS belirleyicisi olduğunu saptadık. Hipoksik geçirilen süre AHI den bağımsız olarak metabolik sendrom riskini artırmaktadır. *Turk Jem 2008; 12: 63-7*

Anahtar kelimeler: Obstruktif uyku apne sendromu, metabolik sendrom, oksijen desaturasyon süresi

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Introduction

Obstructive sleep apnea syndrome (OSAS) is a medical condition characterized by complete or partial obstruction of the upper respiratory airways occurring during sleep (1). The incidence is approximately 4% in adult males and 2% in adult females (2). OSAS is associated with complex hemodynamic changes that are related to systemic hypertension (3), pulmonary hypertension (4), hypercoagulability (5,6), endothelial dysfunction (7), inflammation (8), coronary artery disease (9), insulin resistance (10), and dyslipidemia (9,11). Thus, OSAS can contribute to the development of cardiac and vascular problems. OSAS and metabolic syndrome (MS) share some common features. MS is also a heterogeneous disorder that is associated with insulin resistance (12), diabetes mellitus (13), hypertension (14), dyslipidemia (15), obesity (16), coronary artery disease (17), endothelial dysfunction (18), and hypercoagulability (19). All of these components of MS are known to increase cardiovascular mortality. In Turkey, the prevalence of MS in adults (≥20 years of age) was defined as 35% by METSAR and 37.1% by TEKHARF (20,21) studies.

OSAS is shown to be associated with increased incidence of MS (22). Recently, it has also been proposed that OSAS could represent a component of MS. In this study, we aimed to assess MS prevalence in patients with OSAS and to evaluate the relationship between sleep parameters and MS incidence.

Materials and Methods

Study population and design

Male and female consecutive patients between 20 and 70 years of age and without a prior diagnosis of OSAS, who arrived at the Sleep Disorders Center, Diskapi Yildirim Beyazit Training and Research Hospital Ministry of Health with complaints of snoring, witnessed apnea and excessive daytime sleepiness, were included in this study. The study complied with the Declaration of Helsinki and was approved by the local research ethics committee. All subjects provided written informed consent.

While at the Center, patients underwent polysomnographic (PSG) testing, completed a questionnaire, had physical examinations and blood sample collections.

Questionnaire and physical examinations

A standard questionnaire was administered on the day of PSG testing in order to collect information regarding medical history (including history of sleeping disorders) and family history. A physical examination was also performed. Waist circumference was measured at the narrowest part between the lowest rib margin and the iliac crest with a non-stretchable measuring tape (patients removed all clothing except underwear and were standing for the waist circumference measurements). Weight and height were also measured, and body mass index (BMI) was calculated.

Blood pressure measurements were performed between 8 and 11 a.m. in the right arm with a mercury sphygmomanometer while the patient was sitting in an upright position and following at least 10 minutes of rest. Cigarette smoking and caffeine consumption (coffee, cola etc.) were not allowed for 60 min before the readings. Measurements were performed in both arms and after 5 min, a second measurement was done in the arm with the higher reading. A third measurement was done when the difference between the first and second measurements exceeded 5 mmHg.

Polysomnography and OSAS diagnosis/classifications

Sixteen-channel PSG recordings (electroencephalography, electrooculography, electromyography of chin and leg [anterior tibialis], electrocardiography, oxygen saturation [from finger tips], respiratory effort [thoracic, abdominal] and nasal air flow, body position and tracheal microphone) were obtained for 6-8 hours with the Embla®-flaga instrument. PSG recordings were analyzed by a physician experienced in sleeping disorders by using Somnologica 3.2 software.

Patients with a minimal sleep efficacy of 60% were included in this study. Apnea was defined as complete cessation of airflow for at least 10 seconds, while hypopnea was defined as a 50% decrease in airflow accompanied by development of arousal from sleep or at least a 4% drop in oxygen saturation (criteria proposed by the American Association of Sleep Medicine, 1999). Oxygen desaturation time (ODT) was defined as the duration of time when the oxygen saturation of blood was below 90%. The diagnosis of OSAS was defined by the apnea-hypopnea index (AHI). AHI was calculated by dividing the total number of apnea and hypopnea events during sleep by the total number of hours of sleep. The control group in this study consisted of patients who were classified as normal since they had an AHI <5. The patient group in this study consisted of those with an AHI ≥5. OSAS severity based on AHI was determined as follows: mild (5-14.9), moderate (15-29.9) and severe (≥30).

Blood sample collections

In the morning of the PSG monitoring, venous blood samples were taken for measurements of fasting blood glucose (hexokinase method using Autoanalyser AU5200), triglycerides (glycerophosphate oxidase method using Autoanalyser AU5200), and high-density lipoprotein (HDL) cholesterol (spectrophotometric method using Roche-Hitachi Modular P device).

Diagnosis of metabolic syndrome

The diagnosis of MS was based on the National Cholesterol Education Program criteria (23). An MS diagnosis was made if three or more of the following risk factors were present: waist circumference >88 cm (female) or >102 cm (male); triglycerides ≥150 mg/dL; HDL cholesterol <50 mg/dL (female) or <40 mg/dL (male); blood pressure ≥130/85 mmHg; and fasting blood glucose ≥110 mg/dL.

Statistical analyses

Data analyses were performed with SPSS 13.0 for Windows. The continuous variables were presented as mean ± standard deviation or median (min-max), whereas categorical variables were presented as %. The presence of parametric distribution of the continuous variables was investigated by Shapiro-Wilks' test.

The Student's t or Mann-Whitney tests were used in order to determine if there were any significant differences between groups. A one-way analysis of variance (ANOVA) or the Kruskal-Wallis test were used in order to evaluate the significance of differences in continuous variables between the groups, in the presence of more than two independent groups. In the presence of significant differences, Tukey's multiple comparison where the ANOVA test had been used, and the Bonferroni correction where the Kruskal-Wallis test had used, were performed in order to identify the group(s) that caused the difference. The Mann-Whitney test was also used to perform multiple comparisons.

The significance of a linear relation between the ODT, AHI and MS components was evaluated by Spearman's correlation test.

Chi-square or Fisher's exact test were used for categorical comparison. For the prediction of MS, ROC analysis was done in order to introduce the effect of ODT, and then the area under the curve (AUC), the best intersection point and the sensitivity and specificity levels in this point were calculated. The logistic regression analysis was used in order to examine the multiple effects of variables that have significant effects in the results of mono-variable analysis on the MS. The odds ratio and 95% confidence intervals were calculated. $P < 0.05$ was accepted as statistically significant for the results.

Results

A total of 101 patients were included in the study, with 32 females (31.7%) and 69 males (68.3%). Twenty-one (20.8%) cases with AHI <5 were included the control group, and 80 (79.2%) cases with AHI ≥5 (indicating an OSAS diagnosis) were included the patient group. The demographic features, MS components and MS prevalence of the control and patient groups are shown in Table 1. No significant differences between the patient group and control group were found for age, sex, smoking, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, hyperlipidemia, or coronary artery disease. MS prevalence, waist circumference, triglyceride levels and BMI were found to be significantly higher in the patient group than in the control group. Although systolic blood pressure has a tendency to increase proportionally with OSAS severity, there was no statistically significant difference in blood pressure between the patient and control groups (Table 1).

Table 2 presents the MS prevalence and MS components for the control and patient groups, with the patients divided into three sub-groups according to OSAS severity based on AHI levels (mild=5-14.9, moderate=15-29.9, and severe ≥30). The prevalence of MS in the mild, moderate, and severe OSAS sub-groups were 51.7% (15/29), 77.8% (14/18), and 72.7% (24/33), respectively. The MS prevalence in the control group was only 33.3% (7/21), and the differences in MS prevalences between controls and each OSAS sub-group were statistically significant. No significant correlations were identified between the AHI and any components of MS; however, there was a significant positive correlation between AHI and BMI (rho=0.323, p=0.003).

In Table 3, metabolic parameters are presented for the 80 OSAS patients, divided into two sub-groups according to ODT (<5.75 min and ≥5.75 min). Statistically significant differences between these two ODT sub-groups were found for waist circumference, BMI and MS prevalence. Furthermore, there was a positive correlation between ODT and waist circumference (rho=0.557, p=0.001) and between ODT and fasting blood glucose levels (rho=0.203, p=0.04). We also found that the prevalence of MS showed a statistically significant difference (p=0.005) between the two ODT sub-groups, with an MS incidence of 74.2% (46/62) in patients with ODT ≥5.75, and 38.9% (7/18) in patients with ODT <5.75.

The logistic regression analysis with multiple variables, which was done by inclusion of criteria of AHI ≥5, BMI ≥27 kg/m^2, age and ODT ≥5.75, is presented in Table 4. It was determined that BMI, ODT and age increase the risk of MS independent of other risk factors.

Discussion

In patients with OSAS, there is an increase in cardiovascular risk factors (including endothelial dysfunction, neurohumoral disorders, and systemic inflammation) as well as in hypertension, insulin resistance, impaired glucose tolerance, and dyslipidemia. Because MS also includes these same risk factors, the similarities between these two syndromes were realized, and in 1990 the co-existence of MS and OSAS was named "Syndrome Z" (24).

Table 1. Demographic features, metabolic syndrome components and prevalences

Variables	Controls (N=21)	Patients (N=80)	p value
Age (years)	49.3±11	50.9±9	> 0.05[a]
Sex (male)	66%	68%	> 0.05[b]
Smoking (packet/years)	12 (0-90)	6 (0-90)	> 0.05[c]
BMI (kg/m^2)	28.8±4.3	32.6±6.0	0.008[c]
Diabetes mellitus (%)	0	7.5%	0.198[d]
Hypertension (%)	19%	23.8%	0.490[d]
Coronary artery disease (%)	0	4.8%	0.060[d]
Chronic obstructive lung disease (%)	4.8%	6.3%	0.798[d]
Hypertriglyceridemia (%)	0	0	1
Systolic blood pressure (mmHg)	120.4±19.2	125.0±20.7	0.363[c]
Diastolic blood pressure (mmHg)	83.0±12.9	83.9±13.2	0.796[c]
Fasting Blood Glucose (mg/dL)	107.7±38.2	116.0±43.8	0.428[c]
Waist circumferences (cm)	96.2±14.6	108.2±11.5	< 0.001[a]
Triglyceride (mg/dL)	143.7±55.5	173.0±71.1	0.040[c]
HDL-C (mg/dL)	43.1±9.0	43.3±8.9	0.930[c]
Prevalance of MS (%)	3.3%	66.3%	0.006[b]

BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; MS: metabolic syndrome

[a] Student's t test; [b] Pearson Chi-square test; [c] Mann-Whitney U test; [d] Fisher's Exact test

Table 2. Sleep parameters and components of metabolic syndrome for controls and patients (divided into sub-groups based on OSAS severity)

Variables	Controls (N=21)	Mild OSAS (N=29)	Moderate OSAS (N=18)	Severe OSAS (N=33)
AHI (events/h)[a]	2.3±1.2	9.7±2.7*	21.3±4.9*	63.2±19.5*
ODT (min)a	3.6±5.9	53.5±44.1*	72.9±68.2*	207.0±131.5*
Systolic blood pressure (mmHg)[a]	120.4±19.2	122.2±20.8	124.4±14.6	127.8±23.4
Diastolic blood pressure (mmHg)[a]	83.0±12.9	81.3±11.2	83.0±9.5	86.6±16.2
Fasting plasma glucose (mg/dL)[a]	107.7±38.2	112.4±41.9	119.6±24.5	119.6±53.4
Waist circumferences (cm)[b]	96.2±14.6	105.4±11.5**	109.1±10.6**	110.1±11.9**
Triglyceride (mg/dL)[b]	143.7±55.5	164±62.0	167.5±64.5	183.3±78.7
HDL-C (mg/dL)[a]	43.1±9.0	42.8±8.8	43.0±7.9	43.8±9.8
BMI (kg/m^2)[a]	28.8±4.3	30.5±4.6	31.6±4.4	35.0±7.1***
Prevalance of MS (%)[c]	33.3% (7/21)	51.7% (15/29)	77.8% (14/18)	72.7% (24/33)

OSAS: obstructive sleep apnea syndrome; AHI: apnea-hypopnea index; ODT: oxygen desaturation time; HDL-C: high-densitiy lipoprotein cholesterol; BMI: body mass index; MS: metabolic syndrome
[a] Kruskal-Wallis test; [b] One-way ANOVA; [c] Pearson Chi-square test
*p<0.01 (mild, moderate, severe OSAS vs. control); **p=0.01 (mild, moderate, severe OSAS vs. control); ***p<0.001(severe OSAS vs. control)

Table 3. Sleep parameters and components of metabolic syndrome for controls and patients (divided into sub-groups based on OSAS severity)

Variables	ODT < 5.75 minutes (N=18)	ODT ≥ 5.75 minutes (N=62)	p values
Systolic blood pressure (mm Hg)	118±15.2	126±21.8	0.158[a]
Diastolic blood pressure (mm Hg)	81.1±10.7	84.7±13.9	0.309[a]
Fasting blood glucose (mg/dL)	104.7±26.1	119.3±47.4	0.217[a]
Waist circumferences (cm)	101.2±10.7	110.2±11.0	0.030[b]
Triglyceride (mg/dL)	176.0±65.1	173.2±73.2	0.880[a]
HDL-C (mg/dL)	44.3±11.1	43.0±8.3	0.596[a]
BMI (kg/m^2)	29.0±4.2	33.7±6.11	0.030[a]
Prevalance of MS (%)	38.9% (7/18)	74.2% (46/62)	0.005[c]

ODT: oxygen desaturation time; HDL-C: high-densitiy lipoprotein cholesterol; BMI: body mass index; MS: metabolic syndrome
[a] Mann-Whitney U test; [b] Student's t test; [c] Pearson Chi-square test

Table 4. Logistic regression analysis

Variables	Exp(b)	95% CI for Exp(b), lower-upper	p value
ODT ≥ 5.75 minutes	9.5	1.25-18.21	0.022
Age	2.14	1.23-3.75	< 0.001
BMI ≥ 27 kg/m^2	7.743	1.97-30.41	0.003
AHI ≥ 5 events/h	1.00	0.98-1.02	0.405

ODT: oxygen desaturation time; BMI: body mass index; AHI: apnea-hypopnea index; exp(b): intersection point; CI: confidence interval

There are studies that show that chronic intermittent hypoxemia has a role in the development of metabolic disorders in patients with OSAS. It has been reported that chronic intermittent hypoxemia increases fasting blood glucose levels and disorders in glucose tolerance and insulin resistance via increased sympathetic activation in animal studies (25). It has also been shown that intermittent hypoxia is related to clinical cases of hypertension (26), insulin resistance (27,28), atherogenic dyslipidemia (29), neurohumoral disorders (30), pulmonary hypertension (4), endothelial dysfunction (7), and inflammation (11). In addition, effective treatment of OSAS with continuous positive airway pressure (CPAP) can lead to reduced cardiovascular mortality and morbidity by decreasing chronic intermittent hypoxemia, and thus decreasing sympathetic activity (31), reducing blood pressure and increasing insulin sensitivity. This observation supports the importance of intermittent hypoxemia in the pathogenesis of MS in patients with OSAS.

There are several studies that have evaluated the prevalance of MS and the relative risks by using AHI in patients with OSAS. Coughlin et al found the prevalence of MS to be 83% in patients with OSAS and AHI greater than 15. In a study by Gruber et al, there was a 6-fold increase in the risk of MS (32). Lam et al determined the prevalence of MS to be 37% in patients with an AHI greater than 5, and reported that OSAS causes a 5-fold increase in the risk of MS (33). Lastly, Sasanabe et al also determined an important increase in the prevalence of MS in patients with an AHI greater than 15 (34). Consistent with these findings, data from this current study show that OSAS increases the risk of MS by 9 times.

Also similar to other previous studies, we found increases in BMI, waist circumference, triglyceride levels and MS prevalences in

patients with OSAS. Although there was an increase in systolic blood pressure levels in the patient group compared to the control group, this finding was not statistically significant. However, when patients in this study were divided into sub-groups according to their ODT during sleep, there was a significant increase in MS prevalence, waist circumference and BMI in the patients with ODT ≥5.75. In the multiple logistic regression analysis, in which the criteria of AHI ≥5, BMI ≥27 kg/m^2, age and ODT ≥5.75 were included, it was determined that age, ODT and BMI increased the risk of MS independent of other risk factors; AHI did not cause a significant increase in the risk of MS.

The observation that ODT increases the risk of MS independent of other risk factors is important. Specifically, in patients with mild OSAS (based on AHI), the ODT may be prolonged and reach levels comparable to those in patients with moderate or severe OSAS. In this situation, the risk of MS and the risk of coexisting cardiovascular disease in the mild OSAS patients may actually be greater than anticipated. It has been suggested that ODT is a more reliable parameter than AHI in the determining MS and coexisting cardiovascular disease risks. In one recently published study, patients with OSAS, who had no additional cardiovascular diseases or risk factors, were evaluated for heart type fatty acid binding protein (h-fabp) levels. H-fabp, which is a very sensitive and specific marker of myocardial damage, was found to be higher in the patient group than in the control group. The high h-fabp levels in OSAS patients were related to the ODT spent under 80% and 90% during sleep. There was no relationship between h-fabp levels and AHI. These data support the theory that ODT is more important than AHI in the development of cardiovascular diseases in patients with OSAS (35).

In conclusion, in this study we showed that the increased risk of MS in patients with OSAS is related to the ODT, and is independent of AHI and other risk factors. The time of hypoxia increases the risk of MS and the risk of coexisting cardiovascular disease independent of the current disease classification which is done by AHI. Therefore, it is a rational approach to consider ODT, in addition to AHI, in the cardiovascular risk assessment of patients with OSAS.

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