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INCREASED OXIDATIVE STRESS AND REDUCED ANTIOXIDANT ENZYME ACTIVITY IN OBSTRUCTIVE SLEEP APNEA SYNDROME

Obstrüktif uyku apne sendromunda artmış oksidatif stres ve azalmış antioksidan enzim aktivitesi

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ABSTRACT

Obstructive sleep apnea (OSA) is associated with systemic complications. An increase in hypoxia due to OSA may cause generation of reactive oxygen species (ros) via hypoxia-activated enzyme xanthine oxidase (XO) in the last reactions of the purine catabolism. Another enzyme playing a part in purine metabolism is adenosine deaminase (ADA) which is an important enzyme in the maturation and function of T lymphocytes. ros produced by XO, can reduce antioxidant paraoxonase-1 (PON1). The objective of this study is to determine the activities of XO, ADA, and PON1 activities in OSA patients in comparison with those in non-apneic controls.

The plasma activities of XO, ADA, and PON1 were determined in 57 patients with OSA (apnea-hypopnea index [AHI]) ≥ 15) of whom 19 had cardiovascular disease (CVD), and 38 had OSA but were without CVD and 27 non-apneic controls (AHI ≤ 5). A venous blood sample was obtained early in the morning after the polysomnography night.

XO and ADA activity was found to be significantly higher in the OSA group than the control group. PON1 activity was found lower in the OSA group, but this result was not statistically significant. Min O2 saturation had a significant independent relationship with ADA activity; and AHI had a significant independent relationship with PON1 activity after adjustment for confounding factors that are considered to be related to oxidative stress.

These results support the existence of oxidative stress in OSA and OSA should be considered as a systemic disease.

Key words: Obstructive sleep apnea, xanthine oxidase, adenosine deaminase, paraoxonase-1.

ÖZET

Obstrüktif uyku apne sendromu (OSAS) yaygın sistemik komplikasyonlarla ilişkilidir. OSAS da artmış bir hipoksi durumu pürin katabolizmasının son reaksiyonunda hipoksi ile aktive olan ksantin oksidaz (XO) üzerinden reaktif oksijen türlerinin (ros) açığa çıkmasına neden olabilir. Diğer bir enzim pürin metabolizmasında önemli bir rol oynayan, T lenfositlerinin olgunlaşması ve fonksiyonunda görevli adenosin deaminaz (ADA)'dır. Ros, XO tarafından üretilir ve paraoksonaz-1 (PON-1) seviyesini azaltabilir. Bu çalışmanın amacı OSAS'lı hastalarda XO, ADA ve PON-1 aktivitesini belirlemek ve non-apneik kontrollerle karşılaştırmaktır.

Çalışmaya 57 OSAS'lı hasta (apne hipopne indeksi ≥ 15 ve 19 hastada kardiyovasküler hastalık (KVS) var), 38 KVS hastalığı olmayan OSAS hastası ve 27 kontrol hastası (apne hipopne indeksi ≤ 5) alındı. Grupların XO, ADA ve PON-1 enzim aktiviteleri polisomnografi (PSG) ölçümlerinin yapıldığı gecenin sabahında ölçüldü.

OSAS grubunda XO ve ADA aktivitesi anlamlı olarak yüksek bulundu. OSAS grubunda PON-1 aktivitesi daha düşük bulundu ancak anlamlı değildi. Hasta grubunda minimum oksijen saturasyonu ve ADA aktivitesi arasında ayrıca apne hipopne indeksi ve PON-1 arasında oksidatif stres ile ilgili olduğu düşünülen anlamlı bir ilişki bulundu.

Bulgularımız OSAS da oksidatif stres varlığını desteklemektedir. OSAS sadece nörolojik değil, sistemik bir hastalık olarak göz önünde bulundurulmalıdır.

Anahtar kelimeler: Obstrüktif uyku apne sendromu, ksantin oksidaz, adenozin deaminaz, paraoksonaz-1.

INTRODUCTION

Obstructive Sleep Apnea (OSA) is a condition characterized by repetitive, complete or partial obstruction of the upper airway; often resulting in oxygen desaturation that is normalized when ventilation resumes (1). Associations have been reported between sleep apnea and systemic hypertension, pulmonary hypertension, ischemic heart disease, and stroke (2). The cessation of breathing which leads to hypoxia and reoxygenation may represent a form of oxidative stress, leading to increased generation of reactive oxygen species (ros) that could injure the vascular endothelium and thus may contribute to the association between OSA and cardiovascular disease (3). In addition, OSA has been found to be associated with obesity, inflammation and metabolic dysregulation. All of these indicate that OSA should be considered as a sysystemic disease (4).

Xanthine oxidase (XO), catalyzes the conversion reactions of hypoxanthine to xanthine and xanthine to uric acid, the last reactions in the purine catabolism, with the by product of toxic superoxide radical (5). In this regard, it is a key enzyme between purine and free radical metabolism. Upon reperfusion, XO, in the presence of its substrates hypoxanthine and xanthine, reduces molecular oxygen to $O2^-$ and H2O2, which can further react to the form the more reactive OH^- (6).

Another enzyme playing a part in purine metabolism is adenosine deaminase (ADA). It catalyses the hydroltic deamination of adenosine to inosine and deoxyadenosine to deoxyinosine following dephosphrylation (7). The depletion of adenosine by increased activity of ADA would in turn lead to the accumulation of hypoxanthine and xanthine, which are the substrates of XO (8). The activities of XO and ADA have not been investigated in OSA.

There are various known antioxidant systems against oxidative stress including paraoxonase-1 (PON1). PON1 is an antioxidant enzyme on

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high-density lipoprotein (HDL) that hydrolyses lipid peroxides in oxidized lipoproteins (9). PON1 protects low density lipoprotein (LDL) and HDL from oxidation induced by either copper ion, or free radical generator (10). PON1 activity has been suggested to be inversely associated with oxidative stress in serum and macrophages and serves as an index of free radical mediated damage (11). Reduced PON1 activities have been reported in several groups of patients with diabetes, hypercholesterolemia and cardiovascular disease who are under increased oxidative stres (11,12). Although information on the association between PON1 and OSA is limited, only one report has shown lower circulating PON1 levels in OSA patients with cardiovascular disease (CVD) than on those without CVD or non-OSA controls (13).

Any elevation of XO and ADA, and reduction of PON1 enzyme activities in OSA patients is important to explain their increased prevalence of cardiovascular diseases, and elevation of ADA enzyme activities also for cell-mediated autoimmune disease.

The objective of this study is to determine the activities of purine catabolizing enzymes XO and ADA, and the levels of serum PON1 activities in OSA patients with and without cardiovascular disease in comparison with those in non-apneic controls.

MATERIALS AND METHODS

Subjects

A total of 84 consecutive patients with suspected OSA were recruited from the patients. The diagnosis of OSA was established by full polysomnography (PSG) (Grass Comet ®), and based on the results of PSG, 57 subjects were classified as having OSA (apnea-hypopnea index [AHI]) ≥ 15), of whom 19 had cardiovascular disease (CVD) (hypertension, ischemic heart disease [IHD], or a history of myocardial infarction [MI] or stroke), 38 had OSA but were without CVD and 27 subjects were classified as control group (AHI ≤ 5). Patients with either hypertension, IHD, or a history of MI or stroke were designated as +OSA/+CVD, whereas patients without cardiovascular comorbidity were designated +OSA/-CVD. A diagnosis of hypertension was based on either blood-pressure measurements higher than 140/90 mmHg in both morning and evening measurements or use of antihypertensive medications. A diagnosis of IHD was based on a history of MI or on angiographic findings. The study was approved by the local ethics committee, and all participitants signed an informed consent before being enrolled. Subjects were also asked about their systemic diseases, regular medications and smoking habits.

Anthropometric Measurements

The height, body weight, neck and umbilical circumference were measured on the day when diagnostic PSG was performed. As an indicator of obesity, we used the body mass index (BMI; kg / m2).

Polysomnography

A full night PSG recording was composed of a computerized recording system (Grass Comet ®) which consists of: (1) sleep monitoring through six-channel electroencephalography (EEG; C3/M2, C4/M1, F3/M2, F4/M1, O1/M2, O2/M1), two-channel electrooculography and one-channel submental electromyography (EMG); (2) bilateral tibial EMG and a body-position detector; (3) a two-lead electrocardiogram; and (4) respiration monitoring through a thermistor and nasal cannule for apnea-hypopnea detection, piezo-crystal effort belts for thoraco-abdominal movement detection and a pulse oximeter. Sensors were placed and the equipment was calibrated at the Sleep Laboratory. The sleep recordings were made from 23 00 to 07 00 h. All recordings were scored based on 30 sec epochs according to the Rechtsschaffen and Kales criteria (1).

An overall sleep stage report and accurate measures of respiratory and motor events during the sleeping period were generated. Sleep parameters were assessed based on the sleep recordings. An obstructive apnea was defined as a flat oronasal signal accompanied by respiratory effort movement for ≥10 sec. A central apnea was defined as a flat oronasal signal accompanied by no respiratory effort movement for ≥10 sec. An obstructive hypopnea was defined as a ≥ 50% reduction in the oronasal pressure signal with drop in oxygen saturation by at least 3% from the immediately preceding baseline accompanied by respiratory effort movement, or ≥ 30% reduction in the oronasal pressure signal with drop in oxygen saturation by at least 4% from the immediately preceding baseline accompanied by respiratory effort movement (14,15). The AHI was defined as the number of apnea and hypopneas per hour of sleep. The AHI was calculated and OSA was defined according to the International Classification of Sleep Disorders II. The data were scored by a sleep medicine specialist.

Chemicals

All chemicals used in this study were from Sigma Chemical Co. (St. Louis, MO, USA) and were of analytical grade or the highest grade available.

Samples

All blood samples were collected in the morning after an overnight fast, and serum samples stored at - 70° C until assay for XO, ADA and PON1 activities.

Measurement of XO activity

Serum XO activity was measured by the method of Prajda and Weber, where the activity is measured by determination of uric acid from xanthine. Plasma (50 µL) was incubated for 30 min at 37 0C in 3 mL of phosphate buffer (pH 7.5, 50 mM) containing xanthine (4mM)(27). The reaction was stopped by adding 0.1 mL 100% (w/v) trichloroacetic acid (TCA), the mixture was then centrifuged at 4000 g for 20 min. Urate was determined in the supernatant by measuring absorbance at 292 nm against a blank and expressed as units per milliliter (U/mL) in serum.

Measurement of ADA activity

Plasma ADA activities were estimated spectrophotometrically by the method of Giusti, which is based on the direct measurement of the ammonia produced when ADA acts in excess of adenosine. Results were expressed as units per liter in plasma (U/L) (16).

Measurement of PON1 activity

Serum PON1 activity was measured according to a method described elsewhere (17). We measured the rate of hydrolysis of paraoxon by monitoring the increase of absorbance at 405 nm and at 25°C. The basal assay mixture included 1.0 mM paraoxon and 1.0 mM CaCl2 in 0.05 M glycine buffer pH 10.5. One unit (IU) of paraoxonase activity is defined as 1µmol of p-nitrophenol formed per min, and activity was expressed as U/L of serum.

Statistical analysis

The distributions of all variables were checked by the Kolmogorov-Smirnov test. Independent samples t-test and Mann-Whitney U-test were used to compare demographical and clinical characteristics of the patients and controls. Categorical variables were compared by the $\chi 2$ test.

XO and ADA were compared with the unpaired t test; and PON1 was compared with Mann-Whitney U test.

To investigate correlations between variables, we performed a Pearson correlation analysis; and to determine whether the severity of OSA was independently associated with oxidative stress, multipl regression analyses were performed with XO, ADA and PON1 as the dependent variables. Before the analyses, ln transformation of the data was performed on PON1 and AHI because of the skewed distribution of the data.

Than the subjects were classified into four groups as; control/-CVD, control/+CVD,+OSA/-CVD, +OSA/+CVD. ADA was compared with one-way ANOVA and; XO and PON1 were compared with the Kruskal Wallis test.

All the analyses were two-tailed and were conducted using computer-based statistical software (SPSS ® for Windows 15.0); p value less than 0.05 was accepted as statistically significant.

Results

Based on the results of polysomnography, 57 subjects were classified as having OSAS (AHI ≥ 15), and 27 subjects were classified as control group (AHI ≤ 5). Age, gender, the percentage of CVD, current smokers, hypercholesterol and diabetes were similar between the two groups. However, two groups differed significantly in BMI (p = 0.008), neck and waist circumferences (p = 0.003; p = 0.006, respectively) (Table I).

Characteristics	Controls (n = 27)	OSA (n = 57)	p value
Demographics			
Gender, F / M, n	9 / 18	12 / 45	0.283
Age, yrs	47.6 ± 9.2	47.3 ± 8.8	0.861
BMI, kg / m2	29.0 ± 3.7	31.7 ± 4.4	0.008
Neck circumference, cm	38.7 ± 3.3	41.2 ± 3.1	0.003
Waist circumference, cm	98.9 ± 13.3	108.0 ± 12.5	0.006
Current smokers, %	13	31.6	0.155
CVD, %	33.3	33.3	0.594
Hypercholesterol, %	18.5	36.8	0.129
Diabetes mellitus, %	7.4	12.3	0.712
Diagnostic polysomnography			
AHI	3.1 ± 1.8	42.4 ± 23.5	0.000
Min O2 sat	87.7 ± 4.6	77.2 ± 10.0	0.000

Table I: Demographic and clinical characteristics of patients and control subjects

Data are presented as mean ± SD unless otherwise indicated. OSA: obstructive sleep apnea; F: female; M: male; BMI: body mass index; CVD: cardiovascular disease; AHI: apnea-hypopnea index; min O2 sat: minimum oxygen saturation

XO and ADA activity was found to be significantly higher in the OSA group (p= 0.048, p < 0.001; respectively) than the control group. There was no difference between the OSA and control groups in PON1 activities. (Table II).

	Controls (n = 27)	OSA (n = 57)	p value
XO, U/mL	1.9 ± 0.9	2.2 ± 0.6	0.048
ADA, U/L	22.9 ± 7.2	31.5 ± 12.7	0.000
PON1, U/L	480.4 ± 281.5	417.1 ± 223.4	0.343

Table II: Biochemical data of patients and control subjects

Variables are expressed as mean ± SD, OSA: obstructive sleep apnea; XO: xanthine oxidase; ADA: adenosine deaminase; PON1: paraoxonase

XO and ADA were compared with the unpaired t test; and PON1 was compared with Mann-Whitney U test. All p values are 2-tailed.

Correlation analysis for patients with OSA showed that, AHI was significantly correlated with ADA (r = 0.316, p = 0.004), and PON1 activities (r = - 0.220, p = 0.047), but not with XO activity. However, age and BMI were not correlated with XO, ADA and PON1 activities.

Multiple regression analyses were also performed to examine the independent relationship between oxidative stress and XO, ADA and PON1 activities, with XO, ADA and PON1 activities as the independent variables and AHI, min O2 saturation and confounding factors related to oxidative stress as independent variables (Table III).

These analyses showed that min O2 saturation had a significant independent relationship with ADA activity; and AHI had a significant independent relationship with PON1 activity.

Comparison of the biochemical variables of the four groups (control/-CVH, control/+CVH, +OSA/-CVD, +OSA/+CVD) by one-way ANOVA (for ADA) and Kruskal Wallis test (for XO and PON1) revealed that the four groups differed significantly only in ADA (p = 0.006), The +OSA/-CVD group had higher ADA activity than those of control/-CVH (Table IV).

	Control/-CVD (n= 18)	Control/+CVD (n= 9)	+OSA/-CVD (n = 38)	+OSA/+CVD (n = 19)	p value
XO, U/mL	2.04±0.9	1.6±1.0	2.2±0.7	2.3 ± 0.5	0.262
ADA, U/L	23.2±7.2	22.5±7.6	33.3 ±13.1a	28.0 ± 11.1	0.006
PON1, U/L	440.0±211.2	561.3±389.6	465.4 ± 241.3	309.2 ± 125.7	0.119

Table IV: Biochemical data of controls and patients with and without cardiovascular disease

Variables are expressed as mean ± SD, OSA: obstructive sleep apnea; CVD: cardiovascular disease; XO: xanthine oxidase; ADA: adenosine deaminase; PON1: paraoxonase

ADA was compared with one-way ANOVA and; XO and PON1 were compared with the Kruskal Wallis test. All p values are 2-tailed. a, Significantly higher than those of control/-CVD

DISCUSSION

The current study shows, that the activity of ADA and XO is increased in OSA patients. Although PON1 activity was not different between the OSA patients and control group, AHI was found to have a significant independent relationship with PON1 activity.

Since OSA is characterised by repeated cycles of hypoxia reoxygenation, it was postulated that the hypoxia-activated enzyme xanthine oxidase would create a flux of ros, namely superoxide anions, capable of lipid peroxidation and protein degradation (18). In the vascular endothelium, the XO system is one of the main producers of superoxide anions (19). Elevated levels of XO have been reported in the plasma of patients with respiratory distress syndrome, ischemia and reperfusion injury in many organs, cisplatin-induced nephrotoxicity and major depression (20-23).

The present study is the first study reporting the activity of XO in OSA patients. Although no relationship was found between oxidative stress parameters and XO activity, the XO activity was found to be increased in patients with OSA. The increased XO activity can be an indicator of free radical production in OSA. Repetitive episodes of nocturnal apnea in OSA lead to intermittent hypoxia and recurrent reoxygenation secondary to reperfusion (4). In this case, the activity of this $O2^-$ producer enzyme may increase through the proteolytic conversion of xanthine dehydrogenase to XO and produce an enormous amount of $O2^-$. Enhanced production of ROS, particularly $O2^-$, in OSA patients can be implicated in the pathogenesis of a number of CVD including atherosclerosis, coronary artery disease and hypertension.

ADA has been accepted as an important enzyme in the maturation and function of T lymphocytes. Its main physiological activity is related to lymphocytic proliferation and differentiation (7). The enzyme activity increases substantially during mitogenic and antigenic responses of lymphocytes, and conversly, lymphocyte blastogenesis is inhibited by ADA inhibitors. It is, therefore, known that ADA activity is higher in T cells than B lymphocytes (24). As an indicator of cellular immuni-

	Crude				Adjusted*			
Domain/predicting variables value	B	β	p value	R2	B	β	p	R2
XO								
AHI (ln transformed)	0.043	0.039	0.787	0.001	-0.042	-0.038	0.811	-0.104
Min O2 sat, (%)	0.001	0.019	0.897	0.019	-0.002	-0.029	0.872	-0.072
ADA								
AHI (ln transformed)	2.660	0.124	0.370	0.015	4.020	0.184	0.189	0.052
Min O2 sat, (%)	-0.560	-0.343	0.011	0.121	-0.552	-0.343	0.023	0.141
PON (ln transformed)								
AHI (ln transformed)	-0.282	-0.310	0.021	0.079	-0.260	-0.284	0.043	0.079
Min O2 sat, (%)	-0.005	-0.075	0.592	-0.014	-0.005	-0.074	0.649	-0.030

Table III: Univariate and Multivariate Association Between XO, ADA, PON1 activities and AHI, min O2 sat

*BMI, current smoke, sex, age, cardiovascular disease, hypercholesterol, diabetes mellitus adjusted. B = unstandardized regression coefficient; β = standardized regression coefficient

ty, plasma activity of this enzyme has been suggested to be increased in inflammatory diseases, which causes a cell-mediated immune response (7). Individuals with sleep apnea, also, may be at increased risk for the development, continuation, or aggravation of T-cell mediated autoimmune disease (9). Long-term sleep apnea, via its association with hypoxia-induced hyperuricemia leading to the precipitation of monosodium urate, and the resulting repeated exposure of antigen-presenting cells to epitopes of intracellular origin, may increase the risk of cell-mediated autoimmunity.

The increased activity of ADA activity we found in OSA patients, for the first time, can be another explanation for increased risk for T-cell mediated autoimmune diseases in these patients. The increased activity of ADA in OSA patients depletes the endogenous cardioprotective adenosine levels and leads to the formation of substrates for XO and thus may contribute to the association between OSAS and cardiovascular diseases. Because min O2 saturation had a significant independent relationship with ADA activity and the +OSA/-CVD group had higher ADA activity than those of control/-CVD; it seems that ADA activity is basically correlated with oxidative stress rather than CVD.

PON1 is known, probably via production of super oxide anions produced by XO, to be inactivated by ros. Consumption of PON1 for prevention of oxidation usually leads to variation in serum PON1 activity. Therefore, it can be speculated that superoxide anions could be one of the other responsible factors for decreased PON1 activation, via changing the protein structure. This may exaggerate atherogenesis and, thus, may provide a partial explanation of the high prevalence of cardiovascular morbidity in obstructive sleep apnea patients. Although information on the association between PON1 and OSA is limited, one report has shown lower circulating PON1 levels in OSA patients with cardiovascular disease than on those without CVD or non-OSA controls (13).

We showed in this study that, PON1 activity was not different between the age- and sex- matched OSA and control groups, but AHI was found to have a significant independent relationship with PON1 activity. This finding indicates that PON1 decrease may be related to OSA rather than CVD development.

There are several potential limitations to our study. First, all of the subjects were referred to us with symptoms of OSA and had co-morbidities possibly impacting per se on oxidative stress parameters. We try to match OSA and control group with regard to these confounders. But, the OSA and control group differed significantly in BMI, neck and waist circumferences. Multipl regression analysis was performed to control the influence of obesity and other confounding factors upon the biochemical variables. Second, the study did not evaluate if biochemical changes were reversible after continuous positive airway pressure (CPAP) therapy. Third, this was a cross-sectional study, so we could not assess the causal relationship between OSA and variables.

Our present findings demonstrate a significant increase in XO and ADA activities in OSA patients with a significant independent relationship between min O2 saturation and ADA activity. Although PON1 activity was not different between the OSA patients and control group, AHI was found to have a significant independent relationship with PON1 activity. The findings of this study are potentially significant and add to the growing body of evidence for oxidative stress.

CONCLUSION

Various phenomena are implicated in OSA such as modifications in the autonomic nervous system, hypoxia–reoxygenation cycles, inflammation, and coagulation–fibrinolysis disproportion. Patients with OSA also present increased levels of certain biomarkers linked to endocrine-metabolic and cardiovascular alterations among other systemic consequences. All of this indicates that, more than a local abnormality, OSA should be considered a systemic disease.

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Conflict of Interest
The authors declare no conflict of interest.