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Research Article

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Investigation of the Plasma Nitrite Levels and Oxidant–Antioxidant Status in Obstructive Sleep Apnea Syndrome

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ABSTRACT

Introduction: Obstructive sleep apnea (OSA) is one of the most prevalent sleep disorders. In the present study, we assessed the nitrite level, which is an indirect indicator of nitric oxide (NO), total oxidant status (TOS), total antioxidant status (TAS) and oxidative stress index (OSI), which may be associated with endotel dysfunction. We investigated the difference between the groups and the relationship among the severity of comorbid conditions.

Methods: This study was conducted in 39 OSA patients confirmed by polysomnography and 40 healthy subjects (controls). The OSA group consisted of 10 women and 29 men and the control group consisted of 20 women and 20 men. Polysomnographic revealed mild OSA in two, moderate in 7 and severe in 30 cases. We measured plasma TAS, TOS and nitrite levels from venous blood. The OSI value was obtained by dividing the TOS and TAS values. Values were compared with the control group and between patient groups.

Results: A high body mass index (BMI), cardiovasculer diseases (CVD) and the use of medication for co-morbid diseases were more prevalent in the OSA group (p=.001, p=.029 and p=.006, respectively). The median plasma TOS level and OSI in the obstructive sleep apnea syndrome (OUA) group were significantly higher than those in the control group (p=.001 and p=.001, respectively). The plasma median nitrite level and TAS did not show any significant difference between the OSA and the control groups. None of the parameters revealed a significant difference between severe and moderate OSA cases.

Conclusion: Our findings in the present study revealed that the oxidant–antioxidant balance shifted toward the oxidant side in OSA cases; however, the NO level did not change. These findings together may point out that some molecules other than NO may have a role in the pathophysiology of endothelial dysfunction and also in the disturbed oxidant–antioxidant balance in OSA.

Keywords: Obstructive sleep apnea, nitric oxide, antioxidant, oxidative stress

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS), characterized by repetitive apneas during sleep, is one of the most frequently observed health problems in society (1). It is likely seen together with diseases having a serious risk of morbidity and mortality, such as cardiovascular diseases, hypertension (HT), diabetes mellitus and obesity. There may be numerous factors that facilitate the development of endothelial dysfunction and accordingly, of comorbid conditions, most of which are vascular and metabolic. However, such factors have not been clearly clarified yet. One of the most well-studied and well-known changes is the increased oxidative load. Blood oxygen saturation changes during sleep in OSAS patients may result in the disruption of the oxidant–antioxidant balance in the favor of oxidant molecules depending on recurrent hypoxic periods. In fact, besides sleep apnea, the frequently reported comorbid conditions such as obesity and diabetes mellitus in OSAS patients may also lead to increased oxidative stress (2). Hence, it is not clear whether oxidative stress is a reason for or an outcome of the development of OSAS and complications thereof. However, it can be said that in the light of current knowledge, oxidative stress is a significant aspect shared by all of these clinical conditions.

Nitric oxide (NO) is an important multipotent molecule in endothelial functions. In addition to many different functions, it has a role in the modulation of sleep and circadian rhythm and in the regulation of the cerebrovascular system (3). Changes in plasma NO levels have been reported in many diseases. In particular, cardiovascular and cerebrovascular events may be associated with important changes in NO levels. Any peripheral or central NO changes may be expected in OSAS (4,5). However, the predicted strong connections or correlations between them have not been proved yet.

In this study, we evaluated oxidative stress parameters and plasma nitrite values in OSAS patients and compared them between patient and control groups with regard to the demographic and clinical findings as well as the severity of disease.

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METHODS

Patients over 18 years old without any findings of renal dysfunction, rheumatic disorder, or active infection; who had been pre-diagnosed with OSAS in the Neurology Department of Gaziantep University Medical School and the Neurology Polyclinics of Dr. Ersin Aslan State Hospital; and for whom the diagnosis of OSAS had been confirmed by polysomnography in the Sleep Unit of Dr. Ersin Aslan State Hospital were informed about the study. Thirty OSAS patients consenting to participate in research were included in the study. Polysomnographic recording for patients was performed via a device with Embla N700/somnologica software (Medcare, Iceland). Prior to recording, it was ensured that patients have not used any medicine with disruptive effects on sleep evaluation parameters within the last 15 days. Recordings were performed in all patients during the normal sleep period under standard conditions. The standards of polysomnographic recording were determined on the basis of the AASM Manual for the Scoring of Sleep and Associated Events, WESTCHESTER, IL, 2007 and the results were assessed using the same manual (6). Sleep disorders were evaluated according to the AASM International Classification of Sleep Disorders, Second Edition (7).

The control group comprised 40 voluntary cases without any sleep disorder or neurological disease, as well as any excluding criteria. Sleep disorder in the control group was assessed through face-to-face interviews by doctors experienced in the follow-up of patients with sleep disorders. The time to fall to sleep, the involuntary extremity movements prior to falling to sleep, the average time spent on sleeping, the number of awakenings during night time, the presence of morning headaches, the presence of sleepiness and tiredness and the presence of daytime sleepiness and somnolence were questioned in anamnesis and the Epworth sleep questionnaire was filled by every participant. After the completion of questioning, individuals without any complaints related to sleep were included in the control group.

The study was approved by the Local Ethics Committee of Gaziantep University Medical School and written informed consent form was obtained from all participants. The demographic features, background, family history, physical and neurological examinations, laboratory findings, body mass index (BMI) and sleeping characteristics of the participants were recorded using a questionnaire form.

Blood (10 mL) from brachiocephalic veins of individuals in patient and controls groups was taken and transferred into EDTA tubes containing aprotinin in order to measure plasma nitrite, oxidant and antioxidant levels. The tubes were kept for 15 min with gentle shaking several times and centrifuged at 1600 g/min for 10 min. The obtained plasma samples were stored at −80°C until analysis. Measurements for TOS and TAS were performed with fully automated methods developed by Erel (7,8). Colorimetric and spectrophotometric methods were used for TOS and TAS measurements, respectively. OSI values were obtained by dividing TAS values with TOS values (9). Plasma nitrite levels were determined by ELISA in a TECAN A-5082 Austria device by using a commercial Nitric Oxide (NO_2/NO_3) Research Kit (Enzo Life Sciences, Inc., Catalago No. ADI-917-010).

Statistical Analysis

The Chi-square and Fisher–Freeman–Halton tests were used for the comparison of independent categorical variables. The Fisher's exact test was used in dual-group comparisons. The t-test was used for numerical parameters except for numerical variables without a normal distribution, in which case the Mann–Whitney U test was used. To determine the direction and magnitude of the relationship between numerical variables, the Spearman Rank correlation coefficient was used. The descriptive statistics were shown as number and percent for categorical variables, as mean ± standard deviation for numerical variables with a normal distribution and as median (minimum–maximum) for numerical variables without a normal distribution. The statistically significant level was accepted as a p-value of <0.05. The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) 15.0 for Windows program.

RESULTS

The mean age of the 39 OSAS patients (10 women) in the patient group was 50.46±11.58 years. The mean age of 40 individuals in the control group (20 women) was 53.78±10.20 years.

The mean BMI in patient and control groups were 32±3.18 (minimum–maximum: 24–48) and 28 (minimum–maximum: 22–34), respectively. The BMI of OSAS patients was significantly higher than that of the control group (p=.001). The prevalence of coronary artery disease (CAD) and the rate of medicine use were significantly higher in OSAS patients compared with the control group (p=.029 and p=.006, respectively) (Table 1). By PSG, two mild, seven moderate and 30 severe OSAS cases were identified.

The difference in the comparison between patient and control groups with regard to plasma median nitrite values was not significant (p=.926) (Table 2). Also, there was no significant difference between mild, moderate and severe patient groups when NO levels were evaluated by PSG (p=.485) (Table 2).

In the comparison of plasma NO values according to the background, family history and laboratory findings of patients, a statistically significant negative relationship was observed between NO and BMI in the patient group (p=.018) (Table 3). No difference was found for other parameters.

The results obtained from the comparison of plasma TAS, TOS and OSI values between patient and control groups showed that the difference between the two groups with regard to TAS values was not significant (p=.63) (Table 4) and the TOS and OSI values reported in the patient

Table 1. Backgrounds and sociodemographic features of patients

		Control group (n=40)	Patient group (n=39)	p
Gender (n, %)	Women	20 (50.0)	10 (25.6)	.026[a]
	Men	20 (50.0)	29 (74.4)	
Age (Mean±SD)		53.78±10.20	50.46±11.58	.181[c]
BMI [Median (Min–Max)]		28±3.18 (22-34)	32 (24-48)	.001[d]
Background (n. %)	HT	6 (15)	10 (25.6)	.239[b]
	CAD	1 (2.5)	6 (15.4)	.057[b]
	DM	3 (7.5)	4 (10.3)	.712[b]
	Lung disease	3 (7.5)	5 (12.8)	.481[b]
	Others	10 (25)	9 (23.1)	.842[a]
Medication use (n. %)		3 (7.5)	12 (32.4)	.006[a]

[a]Pearson Chi-square, [b]Fisher's exact test, [c]t-test, [d]Mann–Whitney U test, Min: minimum; Max: maximum; SD: standard deviation; BMI: body mass index; HT: hypertension; CAD: coronary artery disease; DM: diabetes mellitus

group were significantly higher compared with that of the control group (p=.001 and p=.001, respectively) (Table 4).

The comparison of TAS, TOS and OSI values between moderate and severe patient groups by PSG indicated no significant difference (p=.510, p=.877 and p=.383, respectively) (Table 5).

The results obtained from the comparison of plasma TAS, TOS and OSI values according to the background, family history and laboratory findings of patients showed that TAS values of patients with HT were significantly lower compared with that of patients without HT (p=.015). TOS and OSI values of patients with chronic medicine use for any disease were significantly high (p=.001 and p=.003, respectively) (Table 6).

DISCUSSION

Our results of the serum TOS level and oxidative stress index in OSAS patients being significantly high are consistent with literature data. TAS values in the patient group were lower but not significantly different compared with the control group. Plasma median nitrite levels were also not significantly different between both groups. The finding related to the presence of oxidative stress in OSAS patients is supported by several studies (4,10,11). In fact, an increased oxidative stress may be expected in OSAS because of continuous changes in blood oxygen saturation. The consecutive hypooxygenation–reoxygenation periods accompanied by recurrent sleep apneas in OSAS patients may cause endothelial dysfunction and vascular changes as in recurrent ischemia/reperfusion events (12,13). Abnormal central and/or peripheral nitric oxide release is an expected to occur in OSAS patients with endothelial dysfunction and increased oxidative stress (4). However, no strong connection or correlation has been reported yet between NO and OSAS despite a large number of studies on endothelial dysfunction. The reported difference between OSAS patients and control groups with regard to plasma median nitrite levels was also not significant in the present study, although increased oxidative stress was observed in OSAS patients. When all patients were considered collectively in this study, plasma nitrite levels were significantly correlated only with BMI. Therefore, it is important to accurately assess results in order to ensure that BMI values of patient and control groups are identical in studies on NO changes in OSAS. The risk of cardiovascular morbidity and mortality is high in OSAS. The complications associated with OSAS, such as increased sympathetic activity, oxidative stress, changes in baroreflex mechanisms and changes in vascular function, may render patients more prone to cardiovascular diseases (14). However, the underlying reasons have not been clearly clarified yet. In fact, OSAS may be seen together with various clinical conditions that have a disruptive effect on vascular reactivity, such as HT, cardiovascular diseases, metabolic syndrome, or insulin resistance. The presence of comorbid systemic disorders complicates the evaluation of oxidant–antioxidant status, because, as described in previous publications, these disorders that frequently accompany OSAS have a potential to decrease antioxidant capacity and increase oxidant load. Given the composition of our patient group, including more obese patients, a larger number of patients with a history of CAD and a larger number of individuals with chronic medication use compared with the general population, as in most of the previous publications (13,15,16,17), it is possible that our findings appeared as associated with the abovementioned comorbid medical conditions. In our literature search, we found only one study that excludes patients with comorbid diseases. In that study, the impact of the severity of disease on TAS and the effect of overnight continuous positive airway pressure (CPAP) administration on TAS have been analyzed (18). Nevertheless, we think that the difficulties related to evaluations performed in a patient group and the limitations of evaluations focusing on all natural aspects of the disease should also be taken into account considering the high frequency of comorbidities in a natural course of OSAS.

Table 2. Comparison of plasma total nitrite median values between control and patient groups after division into severity subgroups based on PSG results

		Plasma total nitrite levels median [Min–Max (µmol/L)]	p
Patient (n=39)	Moderate	5105 (3563-8721)	p=.485[a]
	Severe	4466.5 (2499-9412)	
	Total	4626 (2499-9412)	p=.926[a]
Control (n=40)	Total	4733 (2552-12710)	

[a]Mann–Whitney U test, Min: minimum; Max: maximum

Table 3. Statistically significant negative relationship between nitrite and BMI

	Nitrite	
	r	*p
Age	-.060	.719[a]
BMI	-.376	.018[a]*

[a]Spearman Rank correlation coefficient. BMI: body mass index, *p<.05

Table 4. Comparison of TAS, TOS and OSI values between patient and control groups

	Control group (n=40) median (Min-Max)	Patient group (n=39) median (Min-Max)	p
TAS	1.63 (.03-4.18)	1.62 (1.06-2.03)	.459[a]
TOS	3.84 (1.29-9.90)	13.12 (2.26-90.45)	<.001[a]*
OSI	.22 (.06-4.20)	.92 (.17-4.39)	<.001[a]*

[a]Mann–Whitney U test, *p<.05. Min: minimum; Max: maximum; TAS: total antioxidant status; TOS: total oxidant status; OSI: oxidant status index

Table 5. Comparison of TAS, TOS and OSI values between moderate and severe patient groups as determined by PSG results

		TAS median (Min-Max)	TOS median (Min-Max)	OSI median (Min-Max)
PSG	Moderate	1.72 (1.25-1.84)	10.72 (2.98-90.45)	.61 (.17-2.32)
	Severe	1.6 (1.06-2.03)	13.94 (2.26-51.46)	1.07 (.18-4.39)
	p	.510[a]	.877[a]	.383[a]

[a]Mann–Whitney U test, *p<.05. Min: minimum; Max: maximum; TAS: total antioxidant status; TOS: total oxidant status; OSI: oxidant status index; PSG: polysomnography

HT is the most frequently seen complication among all cardiovascular complications of OSAS (19). Various epidemiological and experimental studies indicate the presence of a strong connection between OSAS and HT (19,20,21). On the other hand, a large number of studies on OSAS treatment showed that HT could be controlled by OSAS treatment (22,23). However, the calculated mean blood pressure drops in meta-analyses on this subject are statistically significant but were also lower than expected (24,25). This result may have arisen because of the divergent working models of individual studies included in the meta-analyses or because of the differences in HT development mechanisms that could not been completely clarified yet. In our study, patient and control groups were similar with regard to HT. The observation of a normal TAS

Table 6. Results obtained from comparison of TAS, TOS and OSI values according to the background of patients

		TAS median (Min-Max)	TOS median (Min-Max)	OSI median (Min-Max)
HT	No	1.64 (.03-4.18)	5.33 (1.29-50.97)	.36 (.06-4.28)
	Yes	1.43 (1.12-1.92)	8.02 (1.87-90.45)	.60 (.14-4.39)
	p	.015[a]*	.428[a]	.526[a]
Medication use	No	1.64 (.03-4.18)	4.82 (1.29-50.97)	.30 (.06-4.28)
	Yes	1.60 (1.17-2.03)	13.76(2.48-90.45)	1.08 (.14-4.39)
	p	.611[a]	.001[a]*	.003[a]*

[a]Mann–Whitney U test, *p<.05. Min: minimum; Max: maximum; TAS: total antioxidant status; TOS: total oxidant status; OSI: oxidant status index; HT: hypertension

value based on only one measurement as in our study does not exclude the possibility of HT. Therefore, this result may have been obtained because of the limited number of subjects in the study group, the presence of previous HT diagnosis and/or medication use unreported by patients and/or the absence of detailed monitoring of patients for HT. The risk of complication development, the antioxidant status and the response to treatment can vary depending on the severity of OSAS (26,27). The Wisconsin Sleep Cohort study showed that the risk of HT development in OSAS patients with an apnea–hypopnea index of 15 or more is three times higher than that of others irrespective of other factors (28). There was no statistically significant difference between moderate and severe OSAS patients with regard to any parameters in our study. This may be a result of the relatively small size of our patient group and the predominant presence of severe OSAS patients in our study.

The insufficient numbers of mild and/or moderate OSAS patients in our study limited the comparison of the severity of the disease. In this study, OSAS patients were included according to the order of application and the apnea severities of patients were evaluated in further analyses. In other words, the severity of OSAS patients was not one of the criteria used for forming study groups, because the main objective of the study was not to evaluate the impact of disease severity in OSAS patients on the respective parameters but to assess multiple parameters possibly associated with endothelial functions in OSAS patients correlated with endothelial dysfunction. Considering the fact that literature data on studies that have been subjected to evaluations of patients through the said perspective is insufficient, our results may be deemed as preliminary findings. The relatively small size of our patient group, the larger number of women compared to men in our control group, the predominance of severe OSAS patients and the absence of long-term follow-up data are the restrictive aspects of this study. Hence, the need for studies involving wider patient groups and focusing on the evaluation of different conditions associated with endothelial functions by different study protocols is apparent.

Consequently, OSAS, a serious public health problem, is an important condition for both neurological and systemic diseases. Neither the mechanism of OSAS development nor the underlying reason for the frequent appearance thereof together with other systemic diseases has been completely clarified yet. The disruption of the oxidant–antioxidant balance in the course of the disease may have an important role in the underlying mechanisms of the development of both OSAS and complications thereof. Given the information from the current literature, it is a controversial subject that the increased oxidative stress and the decreased antioxidant capacity in OSAS patients are reasons for, or rather outcomes of, the disease because OSAS is accompanied by several clinical conditions increasing oxidative stress as well as actually leading to the development of oxidative stress themselves, such as metabolic syndrome, HT and the like. CPAP therapy can correct certain conditions seen together with OSAS, including HT (29). On the other hand, for example, weight loss declines the severity of OSAS. Therefore, it can be said that there are several complex interactions, which have not been completely clarified yet, between the oxidant–antioxidant balance of the body and the OSAS and other comorbid conditions.

Besides, the incorporation of other factors having a direct or indirect effect on endothelial functions into the researches, as we did in the present study, will widen our perspective. We consider that all studies to be conducted in this regard will help in the clarification of the development mechanism of OSAS, provide important information for both therapeutic and prophylactic medical science and ease the realization of such a health problem that is frequently seen but mostly unnoticed.

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