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The Effects of a Continuous Positive Airway Pressure (CPAP) Therapy on Oxidative Stress in Patients with Obstructive Sleep Apnea

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ABSTRACT

Obstructive sleep apnea (OSA) is a sleep disorder that is prevalent and can have major health consequences. The primary objective of this study was to determine whether oxidative stress is induced in OSA patients. It was further aimed to assess effectiveness of a continuous positive airway pressure (CPAP) therapy on decreasing total oxidant status (TOS) and total antioxidant status (TAS) in OSA patients. This study included 70 patients with sleep disorders. Considering the apnea-hypopnea index (AHI) score confirmed by polysomnography, the subjects were divided into two groups as OSA patients (n = 35) and control group including patients with simple snoring problem (n = 35). OSA patients received a CPAP therapy for one month. Blood samples were collected from both groups of patients to measure TAS and TOS levels before and after the CPAP therapy. TAS and TOS levels were significantly higher ($p < 0.001$), whereas minimum oxygen saturation (minSpO2) and mean oxygen saturation (meanSpO2) were significantly lower in the OSA patients in comparison to those in the control group ($P < 0.001$). Positive correlations were observed between AHI and TAS levels as well as between AHI and TOS levels. Moreover, positive correlations were found between TAS and average stress index (OSI), TOS and OSI, as well as between minSpO2 and meanSpO2. In contrast, negative correlations were observed between AHI and minSpO2 and meanSpO2, and between TAS and OSI, minSpO2 and meanSpO2. One month of CPAP therapy in OSA patients caused a decrease in TAS and TOS levels, and an increase in OSI, minSpO2 and meanSpO2 values ($p < 0.001$). According to the current study, OSA patients have elevated oxidative stress. One month of CPAP therapy seems to have a positive impact on the antioxidant status remarkably, and led to improvement in oxidative stress.

Keywords: CPAP therapy, Obstructive sleep apnea, Oxidative stress, TAS, TOS.

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Introduction

It is well known that obstructive sleep apnea (OSA) is one of the most common sleep disorders which may have serious health consequences. According to the literature data, 9% to 38% of the adult population has OSA with an apnea hypopnea index (AHI) ≥ 5 events/h. OSA is further reported to be more common in men and older age groups [1]. The high incidence of OSA in the population raises serious concerns whether OSA is a public health emergency problem [2]. Thus, it is important to understand physio-pathological mechanisms underlying OSA related diseases.

One of the most frequent pathological abnormalities documented in patients with OSA is hypoxia and hypercapnia. Both conditions are induced by concurrent upper airway collapse occurring as episodes in sleep. Increased respiratory effort and increased sympathetic activity are the concomitant adjustments of the body which may increase the risk of circulatory problems such as cardiovascular diseases and also other health problems like obesity, diabetes mellitus, depression and dementia [3]. It was discovered that elevated oxidative stress is associated with the physio-pathological mechanism behind cardiovascular disorders in OSA patients [4, 5]. High levels of reactive oxygen species (ROS) and an imbalanced mechanism between ROS and antioxidant systems are thought to contribute to microvascular damage in cases of oxidative stress [6]. Moreover, although the pathophysiological mechanisms of OSA have not been completely defined yet, ischemia-reperfusion due to hypoxia episodes cause increased level of ROS and oxidative stress. Those changes may further damage the vascular endothelium [7, 8]. Therefore, treating OSA is crucial to lower oxidative stress and the comorbidities that go along with it. The common clinical practice used in treating OSA is Continuous Positive Airway Pressure (CPAP) therapy [9].

Previous studies report contradictory findings regarding the relationship between oxidative stress and OSA. While the study by Svatikova et al. suggests that increased oxidative stress is not evident in otherwise healthy OSA patients [10], the study by Lavie et al. indicates that oxidative stress is an important underlying cause of cardiovascular diseases in OSA patients [11].Additionally, there is lack of scientific evidence

regarding the changes related to oxidative stress in OSA patients following CPAP therapy. The first aim of this study therefore is to determine total oxidant status (TOS) and total antioxidant status (TAS) levels in OSA patients and compare them with control subjects. It was further aimed to clarify the relationship between oxidative stress and sleep parameters. The second aim was to evaluate into potential changes in TOS and TAS levels following a month of CPAP therapy.

Materials and Methods

Subjects

The Ethical Committee gave its approval to the study's protocol (2017-KAEK-189_2019.09.25_23). The study's subjects included a total of 70 patients who were checked out at the sleep center for OSA. Before the study, each patient provided written informed consent. The subjects had no known comorbidities, and did not use cigarettes or alcohol. Patients were suspected of having OSA if they had one of the symptoms, which include snoring, apnea, excessive daytime sleepiness, or choking during sleep.

Polysomnography

All individuals underwent an overnight polysomnographic examination using a Philips Respironics Alice 6 Sleep Diagnostic System (Germany). The polysomnography consisted of continuous polygraphic recordings of electroencephalography, electrooculography, electrocardiography, and electromyography. Nasal and oral airflow and tracheal sounds were recorded using a microphone. Thoracic and abdominal respiration were measured using an impedance belt. Transcutaneous oxygen saturation of each subject was monitored continuously with a pulse oximeter. Video recordings of the subjects were performed for full-night and positional changes in sleep cycles were recorded. When the test subject awoke in the morning, all recordings associated with the test protocol were stopped. A computerized polysomnographic system and a manual scoring process were used in order to collect the data. Scores for respiratory events were determined using AASM (American Academy of Sleep Medicine) guidelines from 2007 [12]. Accordingly, airflow stopping for at least 10 seconds was used to define apnea. A 30% or greater decrease in airflow lasting for at least 10 seconds along with a perceptible reduction of 4% or more oxygen saturation, a 50% or greater decrease in airflow lasting for at least 10 seconds along with a perceptible reduction of 3% or more oxygen saturation, or an electroencephalogram arousal were all taken into consideration to determine hypopnea.

Two groups were established considering the apnea-hypopnea index (AHI) scores of patients. The AHI was scored as follows: AHI ≥ 5 events/h was defined as OSA (n = 35) and AHI < 5 events/h recognized as control group (n = 35). One month of CPAP therapy (use < 4 h per night and < 5 days per week) was applied to the patients diagnosed with OSA (therapy group, n = 35).

After an overnight polysomnography, fasting morning blood samples from the OSA and control group participants were taken. Same procedure was repeated for the treatment group who came to the control after 1-month of CPAP therapy for analysis of serum TOS and TAS values as well as for calculation of average stress index (OSI) value. The OSI value, which shows the oxidant/antioxidant balance in the organism, is calculated by dividing TOS values by TAS values [13]. Blood samples were centrifuged at 3000 rpm for 10 minutes in a Biobase brand (China) device, and aliquots of serum were kept tightly closed at -20 °C until analysis.

Analysis of the Total Oxidant-Antioxidant Status

An automated colorimetric test approach for TAS developed by Erel [14] was applied to measure the total antioxidant capacity of blood serum. With hydrogen peroxide, the Fe2+-o-dianisidine complex produces an OH radical by a Fenton type reaction. At the reducing low pH, the potent ROS interact with the colorless o-dianisidine molecule to produce yellow-brown dianisidyl radicals. More color is formed as a result of dianisidyl radical participation in additional oxidation processes. Antioxidants present in the samples, however, block these oxidation processes and prevent the development of color. In Biobase Elisa automatic analyzers (Chına), this reaction is monitored spectrophotometrically. In terms of mmol Trolox Eq/L, the TAS results are presented.

An automated colorimetric testing technique developed by Erel [15] was used to measure plasma TOS levels. The ferrous ion-odianisidine complex is converted to ferric ion by the sample's oxidants. This reaction is accelerated by about a threefold factor by the glycerol in the medium. In the acidic media, ferric ions combine with xylenol orange to generate a colorful product. This color is identified spectrophotometrically and is proportional to the amount of oxidant present in the sample. Hydrogen peroxide equivalent per liter (μmol H_2O_2 Eq/L) are used to express the TOS results.

Statistical Analysis

The SPSS for Windows (14.1, SPSS Inc., Chicago, IL, USA) package software was utilized for all statistical analyses. Descriptive statistics for the data were calculated and displayed as 'arithmetic mean ± standard error of mean'. Before the significance tests, the data were analyzed with the Shapiro-Wilk test in terms of conformity to the normal distribution according to the parametric test assumptions. The difference between the control and OSA groups was examined with the Student t test, and the difference in terms of the means before and after CPAP therapy was examined with the paired-sample t test. The relationship between the variables acquired in the OSA group prior to CPAP therapy was examined using Pearson correlation analysis to identify its strength and direction. If a p value for any statistical analysis was less than 0.05, the results were considered significant.

Results

Subjects were divided into two groups as patients diagnosed with OSA (n = 35), and control group with simple snoring problem (n = 35). The average age of OSA patients and the control subjects were 47 ± 1.37 years old and 43.31 ± 1.72, respectively. In both groups, majority of the OSA patients were male (n = 21, 60%). The distribution of age and gender did not significantly differ between groups. Compared to the control subjects, TAS and TOS values were significantly greater whereas OSI levels significantly lower in OSA patients ($p < 0.001$). In comparison to the control subjects, minimum oxygen saturation ($minSpO_2$) and mean oxygen saturation ($meanSpO_2$) were significantly lower in the OSA patients ($p < 0.001$). Table 1 shows the demographics and the parameters of oxidative stress of both groups.

In the OSA patients, one month of CPAP therapy resulted in lower TAS and TOS levels and higher OSI, $minSpO_2$, and $meanSpO_2$ values ($p < 0.001$, Table 2). When patients who received CPAP therapy for 1 month and control subjects were compared, it was observed that CPAP treatment was quite effective and the values of OSA patients approached the values of control subjects, and no statistical difference could be found between these two groups in terms of the parameters examined (Table 2).

Table 1. Comparison of demographic variables and oxidative stress parameters in control subjects and OSA patients

Items	Controls (n = 35)	OSA (n = 35)	p-Value
Age (years)	43.31 ± 1.72	47 ± 1.37	0.098
Gender (male: female)	21: 14	21: 14	1
AHI (events/h)	2.77 ± 0.23	40.46 ± 3.93	< 0.001
TAS (mmol Trolox Eq/L)	0.88 ± 0.02	1.34 ± 0.04	< 0.001
TOS (μmol H_2O_2 Eq/L)	8.19 ± 0.23	9.98 ± 0.22	< 0.001
OSI	0.94 ± 0.02	0.77 ± 0.03	< 0.001
$minSpO_2$ (%)	88.03 ± 0.35	78.97 ± 1.36	< 0.001
$meanSpO_2$ (%)	92.34 ± 0.33	87.71 ± 0.6	< 0.001

Table 2. Comparisons of OSA patients after 1-month of CPAP therapy

Items	Before CPAP	After CPAP	p-Value
TAS (mmol Trolox Eq/L)	1.34 ± 0.04	0.89 ± 0.02	< 0.001
TOS (μmol H_2O_2 Eq/L)	9.98 ± 0.02	8.6 ± 0.03	< 0.001
OSI	0.77 ± 0.03	0.97 ± 0.02	< 0.001
$minSpO_2$ (%)	78.97 ± 1.36	88.09 ± 0.34	< 0.001
$meanSpO_2$ (%)	87.71 ± 0.6	92.43 ± 0.34	< 0.001

Table 3. Comparisons of control subjects and OSA patients after 1-month CPAP therapy

Items	Controls	OSA after CPAP	p-Value
TAS (mmol Trolox Eq/L)	0.88 ± 0.02	0.89 ± 0.02	0.656
TOS (μmol H_2O_2 Eq/L)	8.19 ± 0.23	8.6 ± 0.23	0.203
OSI	0.94 ± 0.02	0.97 ± 0.02	0.195
$minSpO_2$ (%)	88.03 ± 0.35	88.09 ± 0.34	0.908
$meanSpO_2$ (%)	92.34 ± 0.33	92.43 ± 0.34	0.856

Discussion

In our study, we compared polysomnographic records and oxidative stress status of OSA patients with those of the control subjects. We also evaluated the changes in the parameters following a CPAP therapy lasted for 1 month in OSA patients. The specific relationships between physiopathogenic mechanisms in OSA remain unclear. The repeated hypoxia and reoxygenation cycles caused by repeated episodes of breathing cessation during sleep may induce the oxidative stress response which leads to physiopathological changes in OSA patients including metabolic alterations, cardiovascular and neural disorders [16].

A limited number of studies report contradictory results on the TAS/TOS levels in OSA and further on the effectiveness of CPAP treatment to decrease the parameters related to oxidative stress. Kang et al. reported that OSA does not change the TAS and TOS levels and further 1-night of CPAP treatment does not improve the oxidative stress [17]. Similarly, some other authors did not find any differences in parameters indicating increased oxidative stress in OSA patients [10, 11, 18-20]. In contrast, enhanced neutrophil superoxide release [21] and low TAS, vitamin A, and E levels [22] were reported in OSA patients compared with control subjects. In this study, impaired protective systems for oxidative stress were evident in OSA patients. Furthermore, in parallel to findings of the previous study, the higher values of TAS and TOS, and the lower values of OSI noted in OSA group, which suggests that the balance between oxidant and antioxidant levels was negatively affected. Changes in TAS, TOS and OSI show that oxidative stress is evident in OSA patients. These conflicting findings could be caused by a number of variables, including the presence of co-morbidities and the use of drugs by OSA patients. Moreover, most studies lack data from control subjects on different parameters (e.g., body mass index and obesity). The timing of oxidative stress measurements may also affect the results obtained from different studies. All these factors may alter the oxidative stress status of the subjects and are among the limitations of the study. Differentiating the acute and chronic effects of hypoxemia is even more important, as chronic exposure to high oxidative stress may have different effects on oxidative stress parameters in sleep apnea and OSA patients [10].

Discussions over the benefits of CPAP therapy to reduce oxidative stress have been contentious for years. Although some authors reported that CPAP therapy was not effective to decrease oxidative stress as well as the level of antioxidant enzymes [10, 23], other studies demonstrated that CPAP therapy is highly effective to decrease the level of oxidative stress [24, 25]. Kang et al., for example, reported that one night of CPAP treatment had no effect on antioxidant status [17]. In our study, however, it was observed that all parameters (TAS, TOS, OSI, $minSpO_2$, $meanSpO_2$) improved following a long-term therapy with positive airway pressure in OSA patients and approached the values of control subjects. Considering

the parallel findings of this study and the study by Barceló et al. which reported that TAS value returned to normal after 12 months of CPAP therapy [22], one may suggest that positive airway therapy can be effective when conducted for long-term.

In this study, not only TOS but also TAS levels were greater in patients with OSA in comparison to control group in contrast to findings by Barcelo et. al. [22]. Although increased TAS level in OSA patients may be explained by the compensatory mechanism of oxidative stress in the body as stated by Verit and Erel [15], the reasons for these contradictory results regarding TAS and TOS levels should be considered carefully. Some authors suggest that different results related to oxidative stress caused by OSA may be explained by the differences in study protocols such as including/excluding patient with comorbid diseases and treated with drug therapies [17]. To our knowledge, this study is the only study investigating the relationship between oxidative stress and OSA as well as the long-term effect of CPAP therapy on oxidative stress parameters in patients having OSA without any comorbidities while.

In our study, the increase in OSI value after CPAP titration suggests that the balance between oxidant and antioxidant levels is positively affected.

Conclusion

The current study shows that high levels of TAS and TOS, which signify higher oxidative stress, are linked to OSA. CPAP therapy lasted for one-month improved antioxidant status and oxidative stress remarkably. More research is needed to find out the root cause of oxidative stress in OSA patients and its connection to variables like AHI, the length of intermittent hypoxia, the severity of OSA, smoking, as well as to comorbidities like obesity and hypertension. Furthermore, future studies investigating the effectiveness of CPAP therapy in the presence of different factors would contribute to the relevant literature.

Conflicts of interest

There are no conflicts of interest in this work.

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