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The effects of OSAS corrective surgery and anesthesia on inflammatory and oxidative stress parameters in patients with obstructive sleep apnea syndrome

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Abstract

Introduction: Oxidative stress and airway inflammation are important in the pathophysiology of obstructive sleep apnea syndrome (OSAS).

We examined the levels of inflammation and oxidative stress parameters in patients without OSAS and grouped as mild, moderate, and severe OSAS according to the apnea-hypopnea index (AHI). In addition, we investigated the changes in these parameters in patients whose airway obstruction was resolved by surgical treatment.

Materials and method: The groups included 18 patients with an AHI below 5 (group 1), 28 patients with an AHI between 5 and 15 (group 2), 25 patients with an AHI between 15 and 30 (group 3), and 30 patients with an AHI of over 30 (group 4).

Blood samples were collected from patients following the induction of anesthesia (1st measurement), after the operation (2nd measurement), on the postoperative 3rd day (3rd measurement), and at the postoperative 2nd month (4th measurement). Arylesterase (ARE), paraoxonase (PON), nitrotyrosine (NT), leukocyte, CRP, and HDL were measured.

Results: The inter-group comparisons revealed differences in the 3rd measurement of leukocyte count and CRP value, in the 3rd and 4th measurements of HDL ($p < 0.05$). No significant difference was observed in the inter-group or intra-group comparisons for ARE, PON, and NT values ($p > 0.05$).

Conclusion: We observed that CRP, HDL PON, ARE, NT levels, and the leukocyte count were not related to the severity of OSAS in patients with OSAS. The difference observed in CRP and leukocyte count may be due to the continuous effect of the inflammatory effect of surgery in the early post-operative period. We thought that the increase in HDL in all groups after the 5th postoperative day was due to the surgical correction of airway obstruction. As a result, we concluded that CRP, HDL, PON, ARE, NT, and leukocyte levels are not markers for OSAS.

Keywords: Anesthesia, Inflammation, Obstructive sleep apnea syndrome, Oxidative stress

Quick look

Current knowledge

Obstructive sleep apnea syndrome (OSAS) is a clinical picture characterized by continuous obstruction of the upper respiratory tract during sleep. An increase in systemic and biological markers of oxidative stress and inflammation has been reported in patients with OSAS. OSAS surgery is

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one of the treatment methods for OSAS. Oxidative stress and inflammation levels in patients with OSAS have been studied previously, but these levels have not been evaluated after OSAS surgery.

What this paper contributes to our knowledge

We found no difference in CRP, HDL, PON1, ARE levels, and leukocyte counts between patients with and without OSAS. Leukocyte and CRP levels increased only on the 3rd postoperative day. We attributed this height to the continuation of the inflammatory effect of the operation in the early postoperative period. HDL increased in all groups after the operation. We thought that this was due to the surgical removal of airway obstruction in all patients. As a result, we concluded that leukocyte, CRP, HDL, PON1, and ARE cannot be used as markers in the diagnosis and postoperative follow-up of OSAS.

Introduction

Obstructive sleep apnea syndrome (OSAS) is a clinical presentation characterized with continuous obstructions of the upper respiratory tract during sleep. It is observed at a rate of 1–5% among adult men and at a rate of 1.2–2.5% among adult women (Young et al. 1993; Gislason et al. 1993).

Oxidative stress and airway inflammation are both important in the pathophysiology of OSAS and its comorbidity. In OSAS, obstruction in the upper respiratory tract seems to be related to the local inflammation developing as a result of mechanical trauma caused by snoring and to systemic inflammation as well. Examinations of magnetic resonance images have revealed increased inflammation in the sidewalls of the pharynx and related local edema in patients with OSAS (Schwab et al. 1995).

An increase in the systemic and biological indicators of oxidative stress and inflammation in patients with OSAS has been reported (Cofta et al. 2008). Leukocyte count, C-reactive protein (CRP), high-density protein (HDL), nitrotyrosine (NT), paraoxonase (PON), and arylesterase (ARE) values are used to determine the level of inflammation and oxidative stress.

In addition, changes in inflammation parameters were investigated in patients whose airway obstruction was resolved by surgical treatment. For this purpose, leukocyte count, C-reactive protein (CRP), high-density protein (HDL), nitrotyrosine (NT), paraoxonase (PON), and arylesterase (ARE) values were examined in patients.

Materials and methods

Compliance with ethical standards

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (number of the ethics committee: 70904504/141).

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Data available on request from the authors

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patients undergoing surgery due to OSAS were included in the study. Ethical approval was granted by the ethics committee of the hospital. The inclusion criteria were as follows: being between 18 and 65 years of age and being ASA 1–2. The groups included 18 patients with an AHI of under 5 (group 1), 28 patients with an AHI between 5 and 15 (group 2), 25 patients with an AHI between 15 and 30 (group 3), and 30 patients with an AHI of over 30 (group 4). Patients undergoing septoplasty, conchaplasty, uvulopalatopharyngoplasty, radix lingua resection, soft palate reconstruction, and radiofrequency were informed, and consents were obtained.

The demographic data, concomitant diseases, alcohol consumption, and smoking habits were recorded. Standard anesthesia and monitoring methods were applied to the patients, and the operations were performed by the same surgical team. Blood samples were collected from patients after anesthesia induction, after surgery, on the postoperative 3rd day and at the 2nd month. ARE, PON1, NT, CRP, HDL values, and leukocyte count were measured.

Sample collection and storage

Blood samples were centrifuged at +4 °C and 4000 rpm for 4 min. Following serum separation, the samples were kept at − 80.

Biochemical measurements

The PON1 and ARE activities were measured using the Rel-Assay diagnostic paraoxonase and arylesterase activity measurement kit. The serum NT level was measured using the ELISA method and the Rel Assay Diagnostics kit. The serum HDL and LDL levels were measured using the enzymatic-colorimetric method and the Roche Cobas 8000 instrument. The CRP levels were measured using

immunoturbidimetric method and the Siemens Advia 2400 biochemistry autoanalyzer.

Statistical analysis

The categorical variables included in the study were expressed as frequency and percentage. The continuous variables that were compliant to the normal distribution were expressed as mean and standard deviation, and the continuous variables that were not compliant to the normal distribution were expressed as median, minimum, and maximum values. The chi-square test was used for the analysis of the categorical variables. The Kruskal–Wallis test was used for the three-group comparison of variables that did not meet the assumptions of the parametric test. The means of continuous variables were analyzed using the variance analysis (ANOVA) in repetitive measurements, and the Bonferroni correction was performed. The level of significance for differences was accepted at 95% (or $\alpha = 0.05$ error). The biochemical data were analyzed using the IBM SPSS Statistics 18© Copyright SPSS Inc. 1989, 2010 program package. Compliance of the continuous variables to the normal distribution was tested using the Kolmogorov–Smirnov test.

Results

Among 106 patients included in the study, 14 were female (13.2%) and 92 were male (86.8%). The female to male ratio was similar in all four groups ($p = 0.31$). No difference was observed between the groups with regard to the mean age and height ($p = 0.062$ and $p = 0{,}536$, respectively). The mean weight increased from group 1 to 4 ($p = 0.005$). BMI was highest in group 4 ($p = 0.013$) (Table 1).

Seven patients (6.6%) had diabetes mellitus, and 2 patients (1.9%) had asthma. No statistical difference was observed ($p > 0.05$). Fifteen patients (14.2%) had hypertension, which was highest in group 2 ($p = 0.016$). No difference was observed in the history of smoking or alcohol consumption between the groups.

The third measured leukocyte count was found to be elevated compared to all other measurements in all four groups ($p = 0.0001$) (Table 2). No difference was observed between the groups ($p = 0.535$). The 3rd and 4th measurements of HDL were observed to be higher compared to the remaining measurements in all groups ($p = 0.0001$). No difference was observed between the groups ($p = 0.437$) (Table 3). The third measurement of CRP was found to be higher compared to the remaining measurements in all four groups ($p = 0.0001$). No difference was observed between the groups ($p = 0.663$) (Table 4).

No difference was observed between groups with regard to ARE (p: 0.836), PON1 (p: 0.217), and NT (p: 0.456). No difference was observed in the intra-group comparisons either (Tables 5, 6, and 7).

Discussion

Chronic oxidative stress and increased inflammation are responsible for the formation of many chronic diseases (Dyugovskaya et al. 2002; Cakmak et al. 2009). Treatments given to reduce long-term complications in OSAS patients are required to reduce oxidative stress

Table 1 Demographic characteristics and duration of anesthesia and operation in the groups

	Group 1 (*n*: 18)	Group 2 (*n*: 28)	Group 3 (*n*: 25)	Group 4 (*n*: 35)	*p*
Weight (kg)	81.5 ± 10.50	84.44 ± 11.20	86.32 ± 11.35	96.88 ± 20.10	0.005*
Height (cm)	174 ± 7.57	163.68 ± 30.33	173.16 ± 8.49	169.54 ± 21.52	0.536
BMI	27.04 ± 3.74	28.98 ± 3.36	28.80 ± 4.0	31.20 ± 4.44	0.013*
Age (years)	38.9 ± 9.03	46.4 ± 9.99	45.40 ± 9.21	45.3 ± 8.60	0.064

Group 1: AHI: < 5, group 2: AHI: 5–15, group 3: AHI: 15–30, group 4: AH >: 30. *BMI* body mass index. *$p < 0.05$ was accepted as statistically significant. mean ± standard deviation

Table 2 Comparison of leukocyte measurements between the groups

Measurements (BIN/mm^3)	Leukocyte count 1st measurement	Leukocyte count 2nd measurement	Leukocyte count 3rd measurement	Leukocyte count 4th measurement	Mean leukocyte count in groups
Non-OSAS	10.07 ± 3.0	10.24 ± 3.6	13.15 ± 3.8	8.12 ± 1.7	10.40 ± 0.8
Mild OSAS	8.41 ± 2.6	8.86 ± 3.2	13.07 ± 3.7	7.92 ± 1.9	9.57 ± 0.4
Moderate OSAS	7.76 ± 1.7	9.43 ± 2.8	11.75 ± 2.8	7.43 ± 2.3	9.09 ± 0.4
Severe OSAS	8.43 ± 2.0	9.99 ± 2.3	12.76 ± 2.9	7.98 ± 2.7	9.79 ± 0.4
Mean leukocyte count	**8.39 ± 2.2**	**9.54 ± 2.8**	**12.60 ± 3.2**	**7.82 ± 2.3**	

OSAS obstructive sleep apnea syndrome. Group 1: AHI: < 5, group 2: AHI: 5–15, group 3: AHI: 15–30, group 4: AH >: 30

Table 3 Comparison of the HDL levels between the groups

Measurements (mg/dL)	HDL 1st measurements	HDL 2nd measurements	HDL 3rd measurement	HDL 4th measurement	Mean HDL in groups
Non-OSAS	34.55 ± 4.1	32.52 ± 3.5	39.70 ± 4.9	38.84 ± 2.5	36.40 ± 2.7
Mild OSAS	37.27 ± 6.2	32.52 ± 6.8	44.85 ± 6.7	43.14 ± 8.3	40.04 ± 1.7
Moderate OSAS	36.60 ± 10.4	34.90 ± 9.4	49.36 ± 12.4	44.59 ± 13.5	41.48 ± 1.9
Severe OSAS	34.60 ± 35.9	35.38 ± 7.4	44.33 ± 6.2	41.05 ± 6.2	38.46 ± 1.7
Mean HDL	**35.93 ± 6.8**	**33.84 ± 7.3**	**45.18 ± 8.6**	**42.32 ± 8.9**	

OSAS obstructive sleep apnea syndrome. Group 1: AHI: < 5, group 2: AHI: 5–15, group 3: AHI: 15–30, group 4: AH >: 30. Mean ± standard deviation. *HDL* high-density lipoprotein

Table 4 Comparison of CRP levels between the groups

Measurements (mg/dL)	CRP 1st measurement	CRP 2Nd measurement	CRP 3rd measurement	CRP 4th measurement	Mean CRP in groups
Non-OSAS	0.18 ± 0.2	.19 ± 0.2	.87 ± 0.7	.24 ± 0.2	0.37 ± 0.1
Mild OSAS	0.21 ± 0.1	.20 ± 0.1	.64 ± 0.6	.36 ± 0.3	.35 ± 0.08
Moderate OSAS	0.24 ± 0.3	.26 ± 0.3	1.27 ± 0.7	.60 ± 1.3	.59 ± 0.09
Severe OSAS	0.33 ± 0.3	.35 ± 0.3	.80 ± 0.4	.29 ± 0.3	.44 ± 0.08
Mean CRP	**0.25 ± 0.2**	**.26 ± 0.2**	**.88 ± 0.6**	**.38 ± 0.7**	

OSAS obstructive sleep apnea syndrome. Group 1: AHI: < 5, group 2: AHI: 5–15, group 3: AHI: 15–30, group 4: AH >: 30. Mean ± standard deviation. *CRP* C-reactive protein

Table 5 Comparison of ARE levels between the groups

Measurements (U/L)	ARE 1st measurement	ARE 2nd measurement	ARE 3rd measurement	ARE 4th measurement	Mean
Non-OSAS	21.16 ± 2.2	20.75 ± 2.3	21.14 ± 2.7	22.52 ± 3.0	21.39 ± 1.1
Mild OSAS	23.19 ± 7.4	21.09 ± 3.4	21.94 ± 3.0	23.09 ± 3.0	22.33 ± 0.7
Moderate OSAS	20.94 ± 3.4	22.45 ± 8.7	21.63 ± 3.0	21.97 ± 3.6	21.74 ± 0.8
Severe OSAS	22.25 ± 2.5	21.73 ± 2.7	22.61 ± 2.4	23.08 ± 2.4	22.42 ± 0.7
Mean arylesterase	**22.05 ± 4.7**	**21.58 ± 5.0**	**21.96 ± 2.8**	**22.72 ± 3.0**	

OSAS obstructive sleep apnea syndrome. Group 1: AHI: < 5, group 2: AHI: 5–15, group 3: AHI: 15–30, group 4: AH >: 30. Mean ± standard deviation. *ARE* arylesterase

Table 6 Comparison of paraoxonase measurements between the groups

Measurements (U/L)	PON1 1st measurement	PON1 2nd measurement	PON1 3rd measurement	PON1 4th measurement	Mean
Non-OSAS	61.57 ± 37.2	61.56 ± 38.9	62.30 ± 33.6	66.53 ± 37.2	62.9 ± 13.2
Mild OSAS	75.99 ± 46.1	70.89 ± 46.0	76.38 ± 48.6	83.59 ± 54.1	76.7 ± 9.0
Moderate OSAS	52.14 ± 25.2	51.15 ± 26.2	57.43 ± 32.0	50.96 ± 30.9	52.9 ± 9.9
Severe OSAS	52.75 ± 33.9	50.87 ± 35.7	50.83 ± 31.3	53.44 ± 34.7	51.9 ± 9.3
Mean paraoxonase	**61.06 ± 37.3**	**58.68 ± 37.7**	**62.07 ± 38.4**	**64.03 ± 42.5**	

OSAS obstructive sleep apnea syndrome. Group 1: AHI: < 5, group 2: AHI: 5–15, group 3: AHI: 15–30, group 4: AH >: 30. Mean ± standard deviation. *PON1* paraoxonase

and inflammation. For this, it is necessary to evaluate the initial oxidative stress and inflammation levels of the patients and their changes with the treatment given (Dyugovskaya et al. 2002; Cakmak et al. 2009). In this study, it was found that inflammation and oxidative stress did not correlate with the level of systemic biomarkers (mild, moderate or severe) at the onset of the disease treatment in OSAS patients, there was no change in systemic biomarkers with surgical treatment and a significant increase in HDL levels.

Table 7 Comparison of NT between groups

Measurements (ng/ml)	NT 1st measurement	NT 2nd measurement	NT 3rd measurement	NT 4.th measurement	Mean
Non-OSAS	160.55 ± 31.9	191.71 ± 102.6	169.25 ± 13.4	169.73 ± 49.5	172.8 ± 15.8
Mild OSAS	207.09 ± 64.6	193.96 ± 57.7	206.83 ± 55.6	199.04 ± 54.1	201.7 ± 10.5
Moderate OSAS	185.05 ± 42.0	180.0 ± 45.4	209.04 ± 60.0	183.49 ± 49.1	189.3 ± 11.5
Severe OSAS	195.42 ± 47.7	194.06 ± 43.5	195.46 ± 59.9	209.26 ± 57.0	198.5 ± 11.1
Mean nitrotyrosine	**191.48 ± 51.7**	**190.0 ± 58.2**	**198.95 ± 54.8**	**193.70 ± 53.4**	

OSAS obstructive sleep apnea syndrome. Group 1: AHI: < 5, group 2: AHI: 5–15, group 3: AHI: 15–30, group 4: AH >: 30. Mean ± standard deviation. *NT* nitrotyrosine

In this study, the change of CRP and leukocyte counts as inflammatory markers was evaluated

Freire et al. examined the leukocyte count retrospectively in 119 patients diagnosed with OSAS, and no relationship was found between OSAS and leukocyte count (Freire et al. 2010). In this study, there was no difference between the groups in preoperative leukocyte values. Postoperative 3rd day measurement was found to be significantly higher in all groups compared to other measurements. This may be due to the continuation of the surgical effect in the early postoperative period.

Tillet and Francis firstly defined CRP showing precipitation with pneumococcal C polysaccharides in the serum of patients with pneumonia as an acute phase reactant (Tillett and Francis Jr. 1930). It is synthesized from liver cells in response to tissue damage, infection, and inflammation (Whitehead et al. 1983; Castell et al. 1990). Yokoe et al. 2003 found that the CRP levels in patients with OSAS (*n*: 30) were significantly higher than the obese control group (*n*: 14), and a relationship was found between OSAS grade and CRP level. In a study conducted by Shamsuzzaman et al. 2002, CRP levels were found to be significantly higher in patients with OSAS (*n*: 22) compared to the healthy control group (*n*: 20), and it was observed that the CRP level was associated with the degree of OSAS. In this study, no difference was found between the groups with and without OSAS in terms of CRP. In Yokoe et al., unlike ours, the control group was selected from extremely obese individuals, only male patients were included in the study, the OSAS patient group was not classified within itself, and the number of patients was less than our study. In the Shamsuzzaman et al. study, the number of patients was less than the number of our patients, and the patients were selected from patients who had no additional systemic disease and had no OSAS treatment. The different results may be due to these reasons. In the study, CRP was found to be significantly higher in the third measurement than other measurements. This may be due to the continuing inflammatory effect of the operation in the early postoperative period.

In the study, PON, ARE, and NT changes were evaluated as oxidative stress markers

An increase has been reported in the systemic biological indicators of inflammation and oxidative stress in patients with OSAS (Cofta et al. 2008). Barcello et al. reported increased systemic oxidative stress in patients with severe OSAS (Barceló et al. 2006). Reduced antioxidant enzyme activity indicates the presence of systemic oxidative stress in patients with OSAS (Barceló et al. 2006; Christou et al. 2003). Impaired antioxidant defense may exacerbate the deleterious effects of oxidative stress on the vascular endothelium in patients with OSAS (Barcelo et al. 2000).

PON1 and ARE are enzymes in the esterase group, which are encoded by the same gene and whose active centers are similar. PON1 enzyme has an antioxidant function due to its ability to protect LDL from oxidation and to neutralize other radicals, including hydrogen peroxide. ARE is accepted as the indicator of the main protein that is not affected by changes in PON (Li et al. 1993; Ozdin 2002). More than 80% of PON1 circulates depending on HDL (Aviram and Vaya 2013; Deakin et al. 2005). PON1 and ARE are proteins that control oxidative stress (Mackness et al. 1998). PON and ARE activities decrease in chronic inflammatory diseases (Dyugovskaya et al. 2002; Cakmak et al. 2009). Lavie et al. 2004, in his study on 114 patients with OSAS and 30 without OSAS, showed decreased plasma PON1 activity. Baysal et al. (2008) found that PON and ARE activities were lower in OSAS patients compared to the control group ($p < 0.005$).

Unlike ours, Baysal et al. patients with any systemic disease were not included in the study. In the study conducted by Lavie et al., patients with OSAS were divided into patients with and without cardiovascular disease and compared with patients without OSAS. In both studies, patients with OSAS were not grouped according to their severity, as in our study.

NT is formed by the interaction of peroxynitrite and the tyrosine residues of the proteins and may be used as an indicator of potential cytotoxic effects of NO (Alonso et al. 2002). Jelic et al. 2010 reported a correlation between the severity of AHI and NT expression, which

was reduced in patients who had received CPAP for more than 4 h daily. Svatikova et al. 2004 measured the plasma levels of NT at 21.00, prior to sleep, at 06.00 and after waking up, in patients with OSAS. The free NT levels at the baseline were found to be similar prior to sleep between the control and the OSAS groups. No significant difference was observed in plasma NT levels in normal sleep or apneic sleep. The reason for this difference is as follows: in the study conducted by Jelic et al. 2010, volunteers were selected from the community through advertising, and these people were given polysomnography, and those with systemic diseases were not included in the study. In this study, patients who were admitted to our hospital due to snoring and sleep apnea and were scheduled for surgical treatment were selected.

HDL level, which is one of the risk factors for atherosclerosis, was evaluated in our study

There are studies investigating HDL level in OSAS in the literature. Li et al. 2014, in their study on 158 patients, divided the patients into normal primary snoring group (AHI < 5), mild, moderate, and severe OSAS group according to polysomnography. In addition, according to body mass index (BMI), the primary snoring group was divided into normal BMI and overweight (obese) groups. Compared to the primary snoring group, in normal BMI groups, a decrease in HDL was found in the OSAS group. In the study, no difference was found between the groups with and without OSAS in terms of HDL. However, an increase in HDL levels was detected in all groups after the 5th day after OSAS surgery. Increasing HDL level is a highly desirable situation in atherosclerosis prophylaxis and treatment. It would be appropriate to support this increase with other studies.

Conclusion

The relationship between CRP, HDL, PON, ARE, NT values, and leukocyte count with OSAS severity was not found in patients with OSAS. It was concluded that systemic inflammation did not change with OSAS surgical treatment. It was thought that the difference between preoperative and early postoperative CRP and leukocyte measurements might be due to the continuation of the inflammatory effect of the operation in the early postoperative period. In all groups, an increase in HDL was detected after the 5th postoperative day.

Abbreviations

OSAS: Obstructive sleep apnea syndrome; AHI: Apnea-hypopnea index; ARE: Arylesterase; PON: Paraoxonase; NT: Nitrotyrosine; CRP: C-reactive protein; HDL: High-density protein.

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Authors' contributions

İU, KKH, BA, OS, TM, and OKI have contributed in the conception and design of the work, acquisition, analysis, and interpretation of the data and have substantively revised the drafted work. All authors have read and approved the manuscript.

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The design of the study, collection, analysis, and interpretation of data and writing the manuscript was done by the authors without any funding sources to be declared.

Availability of data and materials

All material and data are available.

Declarations

Ethics approval and consent to participate

The Akdeniz University Ethics Committee unit approved the study (number of the ethics committee: 70904504/141). Written consents were obtained from all participants, and consents were recorded.

Consent for publication

Not applicable

Competing interests

The authors declare that there have no competing interests.

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