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Evaluation of the Association of Sleep Apnea-Related Systemic Inflammation with CRP, ESR, and Neutrophil-to-Lymphocyte Ratio

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BDE 1 Mukadder Korkmaz
ABE 1 Hakan Korkmaz
BF 2 Fatma Küçüker
CDF 3 Sema Nur Ayyıldız
CD 4 Soner Çankaya

1 Department of Otorhinolaryngology Head and Neck Surgery, Ordu University Medical School, Ordu, Turkey
2 Department of Pulmonary Diseases, Ordu State Hospital, Ordu, Turkey
3 Department of Biochemistry, Ordu University Medical School, Ordu, Turkey
4 Department of Biostatistics, Ordu University Medical School, Ordu, Turkey

Corresponding Author: Hakan Korkmaz, e-mail: hakankorkmaz@hotmail.com
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Background: Obstructive sleep apnea syndrome (OSAS) is characterized by cyclic episodes of hypoxemia and reoxygenation. It has been suggested that OSAS is associated with chronic inflammation within the microvasculature. This low-grade inflammation may play a role in the pathophysiology of OSAS-related comorbidities. Evaluation of the inflammatory markers may predict the degree of the systemic inflammation and this may be a prognostic factor for future adverse events such as cardiovascular risks. Proinflammatory cytokines have been extensively studied in sleep-disordered breathing. Neutrophil-to-lymphocyte ratio is a recently described indicator of systemic inflammation, but it has not been studied in OSAS patients. In this study we aimed to evaluate the easily measurable parameters of systemic inflammation in these patients. We conducted this study to examine the association among OSAS and C- reactive protein, erythrocyte sedimentation rate, and neutrophil-to-lymphocyte ratio.

Material/Methods: OSAS patients who underwent overnight polysomnography were studied retrospectively. They were divided into 4 groups: control, mild, moderate, and severe OSAS patients. Blood test results and inflammatory markers were compared between the groups. One-way ANOVA and Kruskall-Wallis H test were used for statistical analysis.

Results: A total of 147 patients were included in the study. No differences in evaluated inflammatory markers were observed among the 4 groups.

Conclusions: Evaluation of the OSAS-related systemic inflammation is not likely to be possible by CRP, ESR, or neutrophil-to-lymphocyte ratio measurements. These markers do not seem to be associated with the degree of the upper airway obstruction.

MeSH Keywords: Lymphocytes • Neutrophils • Sleep Apnea, Obstructive • Systemic Inflammatory Response Syndrome

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Background

Obstructive sleep apnea (OSA) is characterized by repetitive pauses in breathing and subsequent hypoxia episodes. Chronic airway collapse and recurrent hypoxia contribute to the development of altered metabolic, immune, and inflammatory system responses [1]. There is some evidence suggesting that OSA is associated with low-level systemic inflammation and oxidative stress [1].

Reports in the literature suggest that obstructive sleep apnea syndrome (OSAS) is the most likely risk factor for the occurrence of renal pathologies, lung diseases, cardiovascular problems, endocrine diseases, diabetes mellitus, and neuropsychiatric diseases [2–4]. Low-level systemic inflammation and subsequent vascular damage has been implicated as the underlying mechanism responsible for these comorbidities [5–8].

Detection of altered inflammatory markers in OSAS patients may predict the degree of nocturnal sleep disturbance and associated systemic inflammation and presence of comorbidities such as cardiovascular diseases and hypertension. Evaluation of inflammatory markers in OSAS patients may be useful for predicting the risk for future comorbidities.

Sleep disturbance-related systemic inflammation alterations can be demonstrated by assessing the level of the inflammatory markers in blood. Repetitive hypoxia-reoxygenation cycles have been shown to be associated with activation of the pro-inflammatory factors IL6, C-reactive protein (CRP), and TNF-α [6,9–13]. Elevated IL6 and TNF-α have been shown to be related to increased cardiovascular morbidity [14,15]. CRP and erythrocyte sedimentation rate (ESR) are widely used inflammatory markers. Recently, novel inflammatory biomarkers such as neutrophil-to-lymphocyte ratio (NLR) have been proposed as indicators of systemic inflammation [16]. NLR is an easily measurable laboratory marker affected by both innate immune response (mediated by neutrophils) and adaptive immune response (mediated by lymphocytes) [17]. Several studies have suggested that an altered NLR has prognostic value in coronary arterial disease, hypertension, diabetes mellitus, cerebrovascular diseases, peripheral arterial disease, chronic kidney disease, and various malignancies [18–24]. To the best of our knowledge, NLR has not been studied in OSAS.

We conducted the present study to evaluate the association between OSAS and the inflammatory markers CRP, ESR, and NLR.

Material and Methods

This multicenter retrospective study was approved by our local ethics committee (OMU-KAEK; 592/2014). Subjects who were referred for polysomnography (PSG) testing and performed the test were included. We reviewed the medical files of patients recorded during 1 November 2012 and 31 December 2013. Venous blood samples were collected from the antecubital vein after 8 to 12 hours of overnight fasting, 1 day before PSG testing. We used Becton Dickinson Vacutainer tubes. Total and differential leukocyte counts were measured within 30 minutes of sampling by an automatic blood counter (Abbott Cell-Dyne Ruby; IL 60064 USA). PSG testing was performed with the Compumedics E series 44 channel PSG device. The PSG recordings included electrocardiography, chest excursions, electroencephalography, and pulse oximetry and leg electromyography. The apnea-hypopnea index (AHI) was defined as the average number of apneas and hypopneas per hour of sleep. PSG data were manually scored. All the patients who underwent overnight PSG testing with available blood sample testing were recruited to the preliminary evaluation. Patients were excluded from the study if they had any malignancy, diabetes mellitus, dyslipidemia, cardiovascular disease or hypertension, chronic inflammatory processes, thyroid dysfunction, chronic hepatic disease, renal failure, or any acute-subacute infectious disease within the past 2 months, and if data such as blood sample testing results were incomplete or if they were unable to undergo complete PSG testing. Data variables included patient age, sex, body- mass index (BMI), apnea-hypopnea index (AHI) score, blood serum variables such as glucose, cholesterol, triglyceride, white blood cell (WBC) count, hemoglobin (Hb), mean corpuscular hemoglobin concentration (MCHC), neutrophil and lymphocyte counts, and inflammatory biomarkers CRP and ESR. NLR was calculated as the ratio of neutrophil count to lymphocyte count. Patients were divided into 4 groups according to PSG results. Group 1, 2, 3, and 4 consisted of patients with AHI scores 0–4, 5–15, 16–30, and more than 30, respectively. Group 1 was considered as not having any sleep-disordered breathing (SDB) problem and they were the control group. To increase the number in the control group, additional subjects were recruited from the hospital records. These subjects were people who applied to the hospital to undergo routine blood screening tests. They were included randomly if they were aged 40 to 50 years and if they did not have any pathology listed in our exclusion criteria. Groups 2, 3, and 4 were mild, moderate, and severe OSAS patients, respectively.

All the data analyses were performed using the Statistical Package for Social Sciences (SPSS) Version 20. The Shapiro-Wilk test was used to evaluate whether data variables were normally distributed. Normally distributed continuos data are expressed as sample size and mean values with standard deviation, and were analyzed by using one-way ANOVA. The Tukey HSD test was used for multiple comparisons. CRP and ESR values were analyzed by using the Kruskall-Wallis H test. $P<0.05$ probability value was considered as significant.

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Table1. Baseline characteristics of the study groups.

	Control	Mild OSAS	Moderate OSAS	Severe OSAS
Age	43.30 (11.14)	44.96 (9.25)	47.24 (9.12)	49.35 (9.79)
Gender	14 M/26 F	18 M/9 F	21 M/16 F	26 M/17 F
BMI	29.27	29.15	31.97	32.60

OSAS – obstructive sleep apnea syndrome; BMI – body mass index; M – male; F – female.

Table 2. Serum laboratory parameters and NLR values of the study groups. The data represent mean values with standard deviations.

	Control	Mild OSAS	Moderate OSAS	Severe OSAS	p
Glucose	98.71 (18.25)	93.15 (11.59)	96.33 (9.61)	99.81 (12.25)	0.190
Cholesterol	194.64 (48.38)	206.73 (39.22)	206.76 (29.97)	200.74 (45.82)	0.646
Triglyceride	145.84 (90.99)	138.35 (58.22)	161.44 (86.86)	160.80 (78.04)	0.602
WBC	6999 (1566)	7751 (2270)	7039 (1550)	7194 (1491)	0.293
Hb	13.94 (1.77)	14.78 (1.49)	14.43 (1.41)	14.73 (1.44)	0.078
MCHC	33.52 (1.21)	33.79 (1.22)	33.44 (1.04)	33.46 (1.19)	0.632
Neutrophil	3977 (1172)	4363 (1698)	3735 (1115)	3865 (1086)	0.240
Lympocyte	2309 (600)	2488 (598)	2448 (587)	2520 (641)	0.429
NLR	1.80 (0.64)	1.78 (0.57)	1.57 (0.54)	1.61 (0.56)	0.223
CRP	0.31 (0.18)	0.40 (0.26)	0.81 (1.94)	0.52 (0.69)	0.135
ESR	14.23 (10.67)	9.69 (8.04)	19.91 (22.32)	15.02 (10.77)	0.433

OSAS – obstructive sleep apnea syndrome; WBC – white blood cell; Hb – hemoglobin; MCHC – mean corpuscular hemoglobin concentration; NLR – neutrophil to lymphocyte ratio; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; p – probability value.

Results

There were 279 patients, including 150 men and 129 women, with a mean age of 51.91 (±9.82) (range: 25–83) who had blood sample values and completed the PSG testing. Based on our exclusion criteria, 161 of them were discarded. The remaining 118 patients were divided into Groups 1 to 4 (according to AHI results), respectively as follows: 11, 27, 37, and 43 patients (Table 1). Additional, 29 healthy subjects were added to the control group as described. Our study group comprised 147 subjects (79 male and 68 female).

Mean blood sample values of the 4 groups and their level of significance are provided in Table 2. The calculated mean values of biochemical markers and complete blood count values listed in Table 2 did not show statistically significant among the 4 groups. Additionally, the mean values of NLR did not show statistically significant levels among the 4 groups. There was no statistically significant difference among groups with respect to median values of other 2 inflammatory markers (ESR and CRP).

Discussion

SDB is characterized by repetitive episodes of upper airway collapse, which causes low-level systemic inflammation [1]. OSAS has been associated with a variety of comorbidities such as cognitive impairment, cardiovascular diseases, pulmonary diseases, endocrine dysfunctions, and neuropsychiatric problems [25–28]. Although the exact mechanism underlying these health problems remain unclear, chronic inflammation has been implicated in their pathogenesis [29–31]. It is not clear if the inflammation is the result or cause of these pathologies, but there seems to be a bidirectional relationship [8]. Detection of inflammatory factors in OSAS patients may help us to predict the risk and severity of the comorbid diseases.

Several inflammatory factors have been studied in SDB patients [32]. In this study, we have evaluated the most widely used and most suitable inflammatory markers in clinical practice.

CRP is an acute-phase protein. It is a nonspecific biomarker of inflammation that is considered as the potential biomarker of

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cardiovascular morbidity. The association between OSAS and CRP levels is inconsistent in the literature. Some studies indicate a relationship between OSAS severity and CRP levels [7,33], while others were unable to demonstrate such a relationship [11]. In our study, there was no correlation between CRP level and AHI scores. There was no statistically significant difference between the control group and the groups of patients with mild, moderate, and severe OSAS.

ESR is a classical inflammatory marker. Its lower sensitivity and specificity and usage of newer inflammatory markers have reduced its value in clinical practice. We have evaluated the variation of ESR in OSAS patients because it is an inexpensive, simple, and widely available parameter. There were no statistically significant difference in ESR values between the control group and mild, moderate, and severe OSAS patients.

The NLR of peripheral blood has been shown to be a marker of systemic inflammation [34]. Evaluation of the NLR in these diseases may help us to predict the progression and prognosis of the disease processes [18,35,36]. Since a variety of diseases, metabolic syndromes, and drugs may affect the NLR, we excluded patients with these comorbidities. We aimed to investigate the association of NLR and OSAS and demonstrate its usability in predicting biochemical alterations. To the best of our knowledge, NLR has not been studied in patients with SDB. Our data revealed that NLR does not show statistically significant alteration in OSAS patients. NLR values did not differ with respect to severity of the SDB and it was similar between control group and OSA patients.

To identify the degree of inflammation in OSAS patients, other inflammatory markers and cytokines (IL6, IL8, TNF-α) can be considered. They are widely studied markers in the literature and generally yield more promising results [1,6]. Additionally, investigation of novel anti-inflammatory markers such as ghrelin can help to predict the pathophysiology and prognosis of the OSAS [37].

Although our study population was large enough to obtain adequate sample size, investigation of the selected parameters in a prospective study with well-designed sampling criteria would be beneficial. A prospective study evaluating CRP, ESR, and NLR levels before and after CPAP application could minimize confounding factors.

Conclusions

The inflammatory markers CRP, ESR, and NLR cannot help us to predict the severity of the level of systemic inflammation in OSAS patients. For this reason, these 3 markers cannot demonstrate the detrimental consequences of OSAS-associated comorbidities, because systemic inflammation and resultant vascular insult is an important underlying mechanism in these diseases. These markers cannot be considered as useful diagnostic and prognostic parameters in clinical practice in OSAS patients.

Conflict of interest

Conflict of interest and source of funding: The authors declare that they have no conflict of interest or any financial support received for this study.

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