

## Serum neopterin, YKL-40, IL-6, and TNF- $\alpha$ in patients with obstructive sleep apnea

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### ABSTRACT

**Objective:** Obstructive Sleep Apnea (OSA) is characterized by recurrent episodes of complete or partial upper airway obstruction during sleep. The role of locally increased inflammation in the upper respiratory tract is known in the pathogenesis of OSA. This study aimed to examine the role of some inflammatory markers in OSA.

**Materials and Methods:** Adult patients who underwent diagnostic polysomnography (PSG) for the first time, were evaluated in this prospective study. Serum levels of neopterin, human cartilage glycoprotein 39 (YKL-40), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- $\alpha$ ) were examined in the study group.

**Results:** The study included 165 adult patients. Individuals of 56 who were did not have OSA were taken as the control group. Patients diagnosed with OSA (n=109) were included in the study and divided into two groups mild-moderate and severe based on the OSA apnea-hypopnea index (AHI). The study groups were divided into 3 categories: AHI <5 (control) Group 1, AHI 5-15 (mild), and AHI 15-30 (moderate) Group 2, AHI>30 (severe) Group 3. Individuals of 165 who completed the study [Group 1 (n=56), Group 2 (n=69), Group 3 (n=40)] were included in the statistical evaluation. There was a significant difference between the groups in terms of neopterin, YKL-40, and IL-6 values (p<0.05). The median value of IL-6 and neopterin measured in the severe group was significantly higher than the value measured in the control and mild-moderate groups (p<0.001). The mean value of YKL-40 measured in the severe group was significantly higher than the value measured in the control group (p=0.012). No significant difference was observed in TNF- $\alpha$  serum levels of groups.

**Conclusion:** Serum levels of neopterin, YKL-40, and IL-6 were found to be elevated in OSA patients (especially in the severe group).

**Keywords:** Obstructive Sleep Apnea, Neopterin, YKL-40, IL-6, TNF- $\alpha$ .

## INTRODUCTION

Obstructive Sleep Apnea (OSA) is a syndrome characterized by recurrent episodes of complete (apnea) or partial (hypopnea) upper respiratory tract obstruction during sleep and often a decrease in blood O<sub>2</sub> saturation [1,2]. Currently, many different types of sleep disorders have been described. Among these, OSA takes the most important place with an average incidence of 1-5% [3].

As a result of apnea and hypopnea periods, hypercarbia and hypoxemia occur, leading to pathologies that affect various organs and systems such as intrathoracic pressure fluctuations, baroreceptor dysfunction, oxidative stress, and endothelial dysfunction [4,5]. The role of locally increased inflammation in the upper respiratory tract is known in the pathogenesis of OSA. It is also believed that hypoxia, asphyxia, hypercapnia, and respiratory acidosis, which occur with a decrease in the intensity of regular breathing that should continue spontaneously, lead to the development of local and systemic inflammation [6,7].

In various studies, increased levels of biomarkers such as C-reactive protein (CRP), interleukin 6 (IL-6), vascular endothelial growth factor (VEGF), leptin, tumor necrosis factor-alpha (TNF- $\alpha$ ), reactive O<sub>2</sub> radicals, intracellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) indicate that systemic inflammation is increased in OSA [8-10].

Neopterin which is a pyrazinopyrimidine compound, is used as a biomarker, especially in important pathologies in which cellular immune mechanisms are activated. An increased concentration of neopterin is associated with all conditions in which the immune response is active, including malignancies and autoimmune diseases [11]. YKL-40 is also a biomarker used in systemic inflammation. It is released from activated macrophage, neutrophils and vascular smooth muscle cells in the inflammatory process. High levels of YKL-40 have been detected in diseases such as atherosclerosis, diabetes, obstructive pulmonary diseases, cancer, and asthma that involve inflammation and tissue remodeling [12]. IL-6 is a cytokine produced in both adipose tissue and skeletal muscle. It is involved in both inflammatory and anti-inflammatory processes. It plays an important role in the pathogenesis of

inflammatory diseases in terms of both its effects on the innate and acquired immune systems and its systemic effects [13]. TNF- $\alpha$  is primarily produced by macrophages. IL-6 and TNF- $\alpha$  are often called proinflammatory cytokines and they contribute to exacerbation of the inflammatory response [14].

In this study, besides the classical markers of inflammation, inflammatory biomarkers that have not yet been used routinely such as neopterin and YKL-40 were also studied. It was aimed to evaluate the importance of inflammatory markers in OSA and whether they would be beneficial in the diagnosis of the disease. Also, it was aimed to evaluate the similarities and differences in inflammatory markers between patients with OSA and individuals without OSA who have the same characteristics features.

## MATERIALS AND METHODS

### Study group

210 adult patients who underwent polysomnography (PSG) for the first time for diagnostic purposes between December 2016 and July 2017 in the Sleep Laboratory of Duzce University Medical Faculty Hospital were evaluated. The patients were taken to the rooms two hours before their usual bedtime, allowing them to get used to the room they would sleep. After connecting the electrodes to the patients, the patients were left alone while all the electrodes were controlled from the computer. Three-channel electroencephalography, two-channel electrooculography, chin, right and left tibialis anterior electromyography, body position, oronasal thermal sensor, nasal pressure sensor, electrocardiography, respiratory sounds recording, thoracic and abdominal respiratory movements, O<sub>2</sub> saturation and synchronous video recording were performed with all-night sleep analysis. All records were scored manually on the computer. 45 of the 210 patients were excluded from the study due to comorbidities. 165 patients with a mean age of  $45.47 \pm 10.4$  years who met the study criteria, were evaluated without gender discrimination. The study group consisted of 49 women and 116 men. In this group, 56 persons who were not found to

have OSA after PSG and met the study criteria were taken as the control group. Patients diagnosed with OSA (n=109) were included in the study in two groups mild-moderate and severe, based on the OSA severity criterion apnea-hypopnea index (AHI) [15]. Persons with an AHI index of <5 after PSG were included in the control group, while patients with AHI $\geq$ 5 were included in the study by grouping among themselves. AHI 5-15 were grouped as "mild", AHI 15-30 as "moderate", and AHI>30 as "severe" OSA. The age, gender, height, and body weight measurements of the people included in the study were made on the night of the sleep test. People were questioned verbally in terms of acute and chronic diseases.

The study was approved by the ethics committee of Duzce University ethics committee (2016/104). Informed consent was obtained from all individual participants included in the study.

### Exclusion criteria

Patients with a diagnosis of diabetes, heart failure, coronary artery disease, chronic renal failure, autoimmune disease, malignancy, inflammatory diseases, chronic lung diseases, or asthma and patients who refused to participate in the study were excluded from the study.

### Biochemical analysis

Patient blood samples were taken just before PSG into serum tubes containing clot activator. After the appropriate amount of sample was left for 20 minutes, it was centrifuged for 10 minutes at 4000xg, the serum was portioned into eppendorf tubes, and stored at -80 °C. The IL-6, TNF- $\alpha$ , neopterin, and YKL-40 tests were studied at once in the fully automatic ELISA device of Triturus (Grifols

Triturus, Spain) using the ELISA (Enzyme-Linked Immunosorbent Assay) method.

### Statistical analysis

Descriptive statistics (mean, standard deviation, median, minimum, maximum) of all variables in the study were calculated. The normality assumption of continuous quantitative variables was checked with Kolmogorov-Smirnov and Shapiro-Wilk tests. One Way ANOVA (post hoc LSD test) was used for the intergroup comparisons of normally distributed variables, and Kruskal-Wallis (post hoc Dunn test) analysis was used for intergroup comparisons of non-normally distributed variables. Relationships between categorical variables were determined by the Pearson Chi-Square test, and relations between quantitative variables were determined by Spearman Correlation analysis. Statistical evaluations were made in the SPSS 22 program and p<0.05 was considered statistically significant.

## RESULTS

165 people were included in the study as three groups. 40 (% 24.3) of them were severe (group 3) OSA, 69 (% 41.8) of them were mild-moderate (group 2) OSA, and 56 (% 33.9) of them were as control group without OSA (group 1). The general characteristics of the patients are summarized in Table 1.

There were no significant differences between the groups in terms of age, gender, and smoking habits (p>0.05). But, it was observed that the measurement values in body mass index (BMI) were significantly different between the groups. The median BMI value of the individuals in the mild-moderate and

**Table 1.** General characteristics of the patients

Characteristic	OSA Group			Total	p
	Control	Mild/Moderate	Severe		
N (%)	56 (33.9)	69 (41.8)	40 (24.3)	165 (100)	
Male (%)	33 (28.4)	51 (44)	32 (27.6)	116 (100)	0.058
Female (%)	23 (46.9)	18 (36.8)	8 (16.3)	49 (100)	0.058
Age (years) mean (min-max)	43.02 (17-65)	46.1 (22-67)	47.8 (26-77)	45.47 (17-77)	0.069
BMI (kg/m <sup>2</sup> ) mean (min-max)	29 (18.3-40.9)	35.9 (22.5-323)	42.3 (17.6-352)	335.04 (17.6-352)	<0.001
% O <sub>2</sub> Saturation mean (min-max)	90 (65-95)	83.9 (71-96)	71.9 (21-92)	83,2 (21-96)	<0.001
Smoking (+) (%)	22 (34.4)	23 (35.9)	19 (29.7)	64 (100)	>0.05
Smoking (-) (%)	34 (33.7)	46 (45.5)	21 (20.8)	101 (100)	>0.05

OSA : Obstructive sleep apnea syndrome, BMI: Body mass index

severe groups was found to be significantly higher than the median value of the BMI measured in the individuals in the control group ( $p < 0.001$ ).

It was determined that the lowest O<sub>2</sub> saturation measurement values were significantly different between the groups. The median value of O<sub>2</sub> saturation of patients in the mild-moderate and severe groups was significantly lower than the value measured in the control group. In addition, the median O<sub>2</sub> saturation value of the patients in the severe group was significantly lower than the value measured in the mild-moderate group ( $p < 0.05$ ).

There was a significant difference between OSA groups at the IL-6 level. The median value of IL-6 measured in the severe group was significantly higher than the value measured in the control

and mild-moderate groups ( $p < 0.05$ ). In the study, as the OSA severity of the patients increased, an increase in IL-6 levels was also noticed (Table 2). No significant difference was observed between the groups in terms of TNF- $\alpha$ .

At the YKL-40 level, there was a significant difference between the groups. The mean value of YKL-40 measured in the severe group was significantly higher than the value measured in the control group ( $p < 0.05$ ). Neopterin level measurements were also found to be significantly different between the groups. The median value of neopterin measured in the severe group was significantly higher than the values measured in the control and mild-moderate groups ( $p < 0.05$ ). As OSA severity increased, the patient's neopterin levels were observed to also be increasing. The serum levels of the studied inflammation markers are summarized in Table 2.

**Table 2.** Comparison of serum levels of IL-6, TNF- $\alpha$ , YKL-40, and neopterin

		OSA Group			Total	p	Post Hoc test	
		Mild-moderate	Severe	Control			Groups compared	p'
IL-6	N	69	40	56	165	<b>&lt;0.001</b>	(Mild-moderate) / (control)	0.001
	Average	43.10	160.88	45.86	72.59			
	Std Deviation	72.74	144.77	60.49	111.13		(Severe) / (control)	<b>&lt;0.001</b>
	Median	114.76	169.30	132.13	143.94			
	Minimum	30	32	44	30		(Mild-moderate) / (severe)	<b>&lt;0.001</b>
	Maximum	331	852	354	852			
TNF- $\alpha$	N	69	40	56	165	0.782		
	Average	0.18	0.20	0.18	0.18			
	Std Deviation	0.21	0.20	0.21	0.21			
	Median	0.13	0.14	0.13	0.13			
	Minimum	0.02	0.01	0.01	0.01			
	Maximum	1.13	0.72	0.87	1.13			
Neopterin	N	69	40	56	165	<b>&lt;0.001</b>	(Mild-moderate) / (control)	0.115
	Average	8.47	9.94	7.53	8.51			
	Std Deviation	3.00	2.84	2.52	2.93		(Severe) / (control)	<b>&lt;0.001</b>
	Median	8.07	9.54	7.03	8.16			
	Minimum	2.74	5.30	2.94	2.74		(Mild-moderate) / (severe)	<b>0.018</b>
	Maximum	17.60	20.20	17.00	20.20			
YKL-40	N	69	40	56	165	<b>0.012</b>	(Mild-moderate) / (control)	0.102
	Average	153.09	176.05	132.21	151.57			
	Std Deviation	72.25	67.28	70.78	72.08		(Severe) / (control)	<b>0.003</b>
	Median	159.00	165.50	130.00	152.00			
	Minimum	5	25	15	5		(Mild-moderate) / (severe)	0.104
	Maximum	302	299	276	302			

## DISCUSSION

Local and systemic inflammation is important in the course of the disease and the occurrence of complications in OSA. It has been observed that increased systemic inflammation is effective in OSA, especially in cardiovascular events [16]. Several studies had shown an increase of numerous inflammation markers such as CRP, leptin, TNF- $\alpha$ , IL-6, VEGF, reactive O<sub>2</sub> radicals, ICAM-1, and VCAM-1 in OSA [8,17]. There are studies showing that TNF- $\alpha$  and IL-6 levels decrease after surgical treatments in patients with OSA. At the same time, the decrease in inflammation biomarkers in parallel with clinical relief after "Continuous Positive Airway Pressure (CPAP)" treatments shows that systemic inflammation is an important factor in the emergence of OSA or as a result of the disease [17,18].

The following results were obtained for O<sub>2</sub> saturation; the lowest O<sub>2</sub> saturation measurement values were significantly different between the groups. The median O<sub>2</sub> saturation value of the individuals in the mild-moderate and severe groups was significantly lower than the value measured in the control group. In addition, the median O<sub>2</sub> saturation value of individuals in the severe group was significantly lower than the value measured in the mild-moderate group ( $p < 0.001$ ) (Table 1).

It was observed that the group with severe OSA had more hypoxic values during sleep (72.73%). Of course, while the patients are awake, their O<sub>2</sub> % saturation is higher. The lowest O<sub>2</sub> saturation parameter that we evaluated in the study is the lowest O<sub>2</sub> saturation measured from the fingertip of the patient during sleep, including recurrent apnea periods. This means that patients with OSA go through severe hypoxic phases during sleep. These fluctuations in O<sub>2</sub> saturation cause hypoxic tissue damage as a result of the recovery of impaired blood O<sub>2</sub> saturation, as in ischemia-reperfusion injury [20]. Intermittent hypoxia observed during sleep initiates systemic inflammation and causes an increase in serum IL-6 level, which is an important proinflammatory cytokine in severe OSA [1]. In a meta-analysis of 39 studies measuring serum IL-6 levels, IL-6 levels of 2558 OSA patients and 1897 control volunteers were examined. It has been reported that serum IL-6 levels were found to be statistically significantly higher in OSA cases [21].

In addition to studies with high serum TNF- $\alpha$  levels in OSA patients, there are also studies with no significant difference [22]. Fornadi et al. found no association between TNF- $\alpha$  and AHI in a study of 100 kidney transplant patients [23]. Similarly, no significant difference was found between the groups with TNF- $\alpha$  in the current study. The serum cytokine levels are dynamic and depends on some conditions: for example, a rapid increase in TNF- $\alpha$  was observed immediately after apnea events [24]. So observing no significant difference in TNF- $\alpha$  can be depending on the time of blood collection.

Otherwise, serum levels of IL-6, YKL-40, and neopterin were found to be significantly higher in the patient groups compared to the control group without OSA ( $p < 0.05$ ). This elevation was more pronounced in the group with severe OSA ( $p < 0.001$ ).

Studies examining serum neopterin levels in OSA patients are few. Ursavas et al. analyzed serum neopterin levels of 22 patients with OSA and 18 patients without OSA. They found no statistically significant difference between patients with and without OSA, but they found that neopterin levels were positively correlated with BMI [25]. In another study, plasma neopterin levels were found to be elevated in hypertensive patients with OSA and were positively correlated with the severity of OSA [26]. In this study the median value of neopterin measured in the severe group was significantly higher than the values measured in the control and mild-moderate groups ( $p < 0.05$ ; Table 2).

In a study by Sui X et al. serum YKL-40 levels were measured in OSA patients by forming two groups with and without coronary artery disease. Serum YKL-40 levels were found to be high in OSA patients with coronary artery disease and also serum YKL-40 levels were correlated with the severity of the disease [27]. There are also different studies stating serum YKL-40 levels may be an indicator of early atherosclerosis in OSA [28]. In a study conducted on 156 patients diagnosed with OSA and 104 healthy volunteers; serum YKL-40 levels were found to be significantly higher in patients compared to the control group, and a positive correlation was found between increased OSA severity and serum YKL-40 levels [27]. Li et al. found YKL-40 levels to be significantly higher in patients with severe OSA. They also found a correlation between serum CRP level, AHI, BMI, insulin resistance, and YKL-40

levels [29]. There is a difference in YKL-40 levels in our severe patient group when compared to mild-moderate and control groups. The mean value of YKL-40 measured in the severe group was significantly higher than the value measured in the control group ( $p < 0.01$ ). Even though the average YKL-40 levels in the mild-moderate patient group differ from those in the control group, this difference did not reach statistical significance ( $p = 0.102$ ).

In a study conducted by Bulcun et al. serum CRP, hs-CRP, IL-6, and TNF- $\alpha$  levels were compared in obese OSA patients (n: 63), OSA patients with normal BMI (n: 49), and control group without OSA (n: 21). As a result, they found no significant difference between the obese and nonobese groups with OSA. Although inflammatory markers were high in patients with OSA, there was no statistically significant difference from the group without OSA [30]. The statistically significant difference in terms of BMI in the patient groups we selected is the inevitable result of the very common association between obesity and OSA. BMI is higher than in other groups, especially in group 3; where there are patients with severe OSA. However, the fact that obesity is an independent risk factor for OSA, and that inflammation increases as OSA and weight increases (in correlation with AHI) independently of obesity in various studies suggest that high BMI in patient groups does not adversely affect our study [30].

Vgontzas et al. studied serum IL-1 $\beta$ , TNF- $\alpha$ , IL-6 levels in OSA, narcolepsy, and hypersomnia. They found that serum TNF- $\alpha$  levels were significantly higher in OSA and narcolepsy, associated with excessive daytime sleepiness. Serum IL-6 level was found to be significantly higher only in OSA and it was shown to be correlated with BMI. When IL-6 and TNF- $\alpha$  were given to individuals, increased sleep desire and weakness occurred; suggesting that these two cytokines mediated the main symptoms of OSA with these findings. The same researchers found IL-6 and TNF- $\alpha$  to be high in obese individuals with OSA. However, they showed that high cytokine levels in OSA are factors independent of tissue adiposity and insulin resistance [31,32].

In this study, no significant difference was found between the groups in terms of age, gender, and smoking habits. There were approximately similar proportions of smokers and non-smokers in all

three study groups. The handicap that we had in this regard was that the exposure times of patients who smoke had not been evaluated in the study, and patients who quit smoking had also been evaluated as active non-smokers, despite having previously been exposed to tobacco. With a more comprehensive study, the relationship between OSA smoking and inflammation can be evaluated by considering the smoking history and exposure time of the patients. In this study, the inflammatory markers investigated were compared between the OSA groups and the relationship between AHI or BMI and inflammatory markers was not examined. This is another limitation of the study.

There are serious complications and increased mortality in OSA with AHI > 20 and above. As can be seen in the studies, the presence of subclinical inflammation increases as the severity of OSA increases, and the risk of complications increases. Inflammation, which is one of the factors that should be blamed for the aggravation of OSA and the development of complications, may also play a key role in the treatment. Further on it is a big problem that CPAP and other devices used in the treatment of OSA today are difficult to use and provide palliative treatment. When patients can not use or refuse to use their devices, there are no treatment alternatives available. In addition to being able to diagnose patients with OSA, the predictability of possible complications is also important for patient survival and quality of life. For this reason, it seems that biochemical-based studies can be a light for understanding the pathophysiology of OSA, producing alternative options for its' treatment and prevention of complications.

In conclusion, local and systemic inflammation has an important role in the course of the disease and the emergence of complications in OSA. In particular, there is increasing evidence that inflammation plays a major role in the cardiovascular pathophysiology of OSA. In the light of these data, more studies are needed on the place of inflammation in the diagnosis and treatment process of OSA, whether or how inflammatory markers can be used in diagnosis and treatment follow-up. In this study, a general and broad view of the subject was aimed by evaluating the newly found markers thought to be an indicator of inflammation and classical markers of inflammation together.

### Author contribution

Study conception and design: ÖA, İEŞ, and EGB; data collection: ÖA; analysis and interpretation of results: ÖA and ŞÇ; draft manuscript preparation: ÖA, İEŞ and EGB. All authors reviewed the results and approved the final version of the manuscript.

### Ethical approval

Ethics committee approval was received for this study from the ethics committee of Duzce University

(2016/104). Informed consent was obtained from all individual participants included in the study.

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### Conflict of interest

The authors declare that there is no conflict of interest.

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