CLINICAL STUDY

INTERLEUKIN-6, INTERLEUKIN-10 AND TUMOR NECROSIS FACTOR-α PLASMA LEVELS IN OBSTRUCTIVE SLEEP APNEA

Oğuz KUŞCU, MD; Taner YILMAZ, MD; Tevfik SÖZEN, MD; Oğuz ÖĞRETMENOĞLU, MD

Hacettepe Üniversitesi Tıp Fakültesi KBB Anabilim Dalı, KBB, Ankara, Turkey

SUMMARY

The aim of this prospective clinical trial is to investigate plasma IL-6, IL-10, TNF α levels in patients with Obstructive Sleep Apnea Syndrome (OSAS).

TNF-α, IL-6 and IL-10 were measured in plasma of patients with OSAS. OSAS group with Apnea Hypopnea Index (AHI) ≥5, 42 patients and control group with AHI<5, 40 patients.

Plasma levels of IL-6 were statistically significantly higher in OSAS patients, and increased significantly as severity of OSAS increased. Mean IL-10 plasma levels of OSAS patients was statistically significantly lower than that of control group and decreased significantly as severity of OSAS increased. Mean plasma TNF-α level did neither differ significantly between OSAS and control groups, nor did it change significantly as severity of OSAS increased. Linear regression revealed plasma TNF-α level as the only significant independent factor influencing plasma IL-6 level. IL-6 increased as TNF-α increased. According to linear regression, no factor influenced plasma IL-10 level independently. Age was the only significant independent factor determining TNF-α. TNF-α increased with increasing age.

Increase in pro-inflammatory cytokine, IL-6, and decrease in anti-inflammatory cytokine, IL-10, in OSAS patients may have important health consequences. Therefore, we suggest that these two cytokines be measured in patients with OSAS, especially in males, before planning treatment, because they give information about systemic damage imposed by OSAS.

Keywords: Interleukins; interleukin-10; interleukin-6; sleep apnea, obstructive; cytokines; tumor necrosis factor-alpha

TIKAYICI UYKU APNESİ SENDROMUNDA PLASMA İNTERLÖKİN-6, İNTERLÖKİN-10 VE TÜMÖR NEKROZİS FACTOR -α DÜZEYLERİ

ÖZET

Bu klinik çalışmada Tıkayıcı Uyku Apnesi Sendromunda(TUAS) plasma IL-6,IL-10 ve TNF-α düzeylerinin araştırılması amaçlanmıştır.

Yapılan Polisomnografik sonuçlarına göre Apne-Hipopne indeksi (AHI) 5 ve üzerinde olan 42 hasta ile AHI 5'in altında olan 40 hasta kontrol grubu olarak ele alınmıştır. Her iki gruptaki hastaların plasma IL-6,IL-10 ve TNF-α düzeyleri saptanmıştır.

Plasma IL-6 düzeyi TUAS grubunda kontrol grubuna kıyasla istatistiksel olarak anlamlı derecede yüksek saptanmakla beraber hastalık şiddeti ile doğru orantılı olarak artış göstermektedir. Ortalama plasma IL-10 düzeyi TUAS grubunda kontrol grubuna göre anlamlı dercede düşük olarak saptanmakla beraber hastalık şiddeti ile ters orantılı olduğu saptanmıştır. Plasma TNF-α düzeyi TUAS ile veya hastalık şiddeti ile istatistiksel olarak herhangi bir değişim göstermemiştir. Lineer regresyon testinde TNF-α'nın bağımsız faktör olarak sadece IL-6 düzeyinden etkilendiği saptanmıştır. Il-6 düzeyi arttıkça TNF-α düzeyinin de artmakta olduğu saptanmıştır. IL-10 düzeyini bağımsız olarak etkileyen herhangi bir faktör saptanmamıştır. Ayrıca TNF-α düzeyinin yaşla ile korrele olduğu saptanmıştır.

İnflamatuar sitokinlerden IL-6 düzeyinin artması ve IL-10 düzeyinin azalmasının TUAS olan hastalarda önemli sağlık sorunlarına yol açabileceği aşikardır. Bu yüzden bu iki sitokinin TUAS'daki olası sistemik hasardan sorumlu olması dolayısıyla TUAS olan hastalarda ölçülebilir bir parametre olarak rutin kullanıma girmesi ve özellikle erkek hastalarda tedavi planlanmasında kullanılması bu çalışma tarafından önerilmektedir.

Anahtar Sözcükler: İnterlökinler;interlökin-10;interlökin-6; uyku apnesi, tıkayıcı; sitokin; tümör nekrozis faktör-alpha

INTRODUCTION

Obstructive sleep apnea (OSA) is a fairly common condition characterized by repetitive airway collapse during sleep, as well as daytime sleepiness. OSA affects 2% to 4% of middle aged adults. A narrow upper airway is noted in all age groups and probably predisposes to airway collapse during sleep. Despite the known anatomic factors such as cranifacial anomalies, obesity, adenotonsillar hypertrophy and loose soft palate that contribute to OSAS, a clear anatomic factor cannot always be identified[1].

Obstructive Sleep Apnea Syndrome affects mainly the working age population and has been found to be independently associated with pro-inflammatory cytokines. The most relevant findings in OSAS patients are increased tumor necrosis factor (TNF)-α and interleukin (IL)-6 secretion from peripheral mononuclear cells stimulated with lipopolysaccharide, as well as the increase in plasma levels of these two pro-inflammatory cytokines compared to control subjects. Their levels have been significantly correlated with the percentage of time of apnea and hypopnea, as well as the percentage of time spent at oxygen saturation (S_{O2}) below 90% during the total sleep period[2].

Corresponding Author: Oğuz Kuşcu MD Hacettepe Üniversitesi Tıp Fakültesi KBB Anabilim Dalı, KBB, Ankara, Turkey, E-mail: drkuscu@gmail.com

Received: 09 November 2015, revised for: 22 November 2015, accepted for publication: 22 November 2015

Upper airway obstruction causes apnea or hypopnea and consequently hypoxemia and acidosis. Chronic hypoxemia has a role in hypertension, arrhythmia, and pulmonary hypertension[3]. The pathogenesis of cardiovascular complications in OSAS is not completely understood; evidence suggests that increased levels of various circulating inflammatory factors, including TNF-α, IL-6 and IL-8, are associated with future cardiovascular risk. Inflammatory responses may therefore play a pivotal role in the pathogenic process of cardiovascular complications associated with OSAS through inflammatory-factor-mediated arterial endothelial cell dysfunction[4]. The aim of this study was to evaluate chronic inflammation in OSAS patients by measuring plasma cytokine levels such as IL-6, IL-10 and TNF-α.

MATERIAL and METHODS

This prospective study was approved by the institutional ethics committee of XXX University Faculty of Medicine (approval identification number:LUT09/31-4). Informed consent was obtained from each patient before entering the study. 82 patients at and over the age of 18 with a complaint of snoring and/or apnea-hypopnea underwent sleep polysomnography (PSG).

According to PSG results, 42 patients were assigned to the OSAS group (AHI≥5) and 40 patients who had AHI<5 were assigned to the control group. The overnight PSG was performed according to the Guidelines of the American Electroencephalographic Society (1994) and included the following parameters: electroencephalography (EEG), electroculographic activity, submental electromyographic activity, intercostal electromyographic activity, chest and abdominal movements, snoring, airflow (oronasal flowmetry), oxygen saturation and plethysmography, lower limb movement and electrocardiographic activity. The 8-h polysomnogram was performed by a certified sleep technician and was scored and interpreted by a certified physician according to standardized criteria.

OSAS diagnosis was based on the Criteria of the International Classification of Sleep Disorders (American Sleep Disorders Association, 1990). Obstructive apnea was defined as a cessation of air flow for at least 10 s in the presence of a respiratory effort despite cessation of airflow. Hypopnea occurred when there was a reduction of airflow by 50% or more for at least 10 s. The number of apnea or hypopnea events per hour was obtained by dividing the total number of such events to total sleep time as defined by the AHI.

Blood samples were collected from all patients (OSAS and control group) in the morning between the hours of 8:00 a.m. and 9:00 a.m. after PSG. 10 ml of blood was collected in tubes containing EDTA. They were centrifuged at 1700 x gravity for 10 min and plasma was stored at -80° C. IL-6, TNF-α, and IL-10 were determined in plasma samples using commercially available enzyme-linked immunosorbent assay (ELISA) kits.

Statistical Analysis

All data were statistically analyzed using SPSS 15.0 for Windows. The following statistics were used: Student's t-test for independent samples, analysis of variance, chi-square test, correlation analysis, linear regression. Significance was taken as $p<0.05$.

RESULTS

On a total of 82 patients (42 diagnosed with OSA and 40 controls with simple snoring) blood cytokine levels were measured. The mean age was 48 for the OSAS group and 46 for the control group. The difference between ages was not statistically significant (Student's t-test, t=0.876, p=0.643). 25 females (12 OSAS patients, 13 control patients) and 57 males (30 OSAS patients, 27 control patients) were included in this study. The difference between sex ratios of both groups was not statistically significant (Chi-square test, $\chi 2= 0.15$, p=0.70).

This study included 9 patients with mild, 14 patients with moderate and nineteen patients with severe OSAS. The mean BMI was 30.2±7.8 for the OSAS group and 29.7±4.9 for the control group. This difference was not statistically significant (Student's t-test; t=1.925, p=0.11). Mean time spent with O^2 saturation (S_{O2}) below 90% was 16.3 % of the total sleep period for the OSAS group and 3.3 % for the control group. This difference was statistically significant (Student's t-test; t=4.769, p=0.003) (Table 1).

To investigate the possible association between the inflammatory biomarkers and the severity of OSAS, the whole study population was divided into four different groups according to AHI level (Table 2). It was found that IL-10 showed a significant decline in conjunction with increasing AHI (Analysis of variance; F=3.745, p=0.002). IL-6 levels showed a significant increase in conjunction with increasing AHI (Analysis of variance; F=5.876, p=0.001). TNF-α showed no significant changes according to AHI (Analysis of variance; F=0.836 p=0.48) (Table 2).

BMI was grouped as normal (BMI≤25), overweight (2530). IL-6, IL-10 and TNF-α levels were not significantly different among BMI groups (p>0.05) (Table 3)

IL-6

The mean plasma IL-6 levels were 4.68±0.24 pg/ml in the OSAS group and 0.92±0.02 pg/ml in the control group. This difference was statistically significant (Student's t-test; t=6.925, p=0.008).

Within the OSAS group, male patients' mean plasma IL-6 level was 5.47±2.81 pg/ml and female patients' IL-6 level was 1.90±0.13pg/ml; this difference was statistically significant (Student's t test, t=4.786, p=0.003). In the control group, male patients' mean plasma IL-6 level was 1.02±0.41 pg/ml and female patients' mean plasma IL-6 level was 0.89±0.26 pg/ml; this difference was not statistically significant (Student's t test, t=0.759, p=0.214).

Plasma IL-6 levels showed significant changes with respect to apnea position. For patients who had non-positional apnea on PSG mean plasma IL-6 level was 5.6±1.7 pg/ml and for patients with positional apnea mean IL-6 level was 0.9±0.3 pg/ml; this difference was statistically significant (Student's t-test, t =7.565, p=0.001). All results about IL-6 were summarized in Table 4.

Linear regression was performed to identify independent factors influencing plasma IL-6 level. Dependent variable was plasma IL-6 level. Independent factors were age, sex, BMI, AHI, time S_{O2}<90%, IL-10, TNF-α, position dependence of apnea. Plasma TNF-α level was determined as the only significant independent factor (t=2.053, p=0.043). IL-6 increased as TNF-α increased.

IL-10

The mean plasma IL-10 levels were 0.82±0.54 pg/ml in the OSAS group and 1.94±0.73 pg/ml in the control group. This difference was statistically significant (Student's test, t= 2.325, p=0.007). Plasma IL-10 levels of patients with positional and non-positional apnea were not significantly different (p>0.05). Males in the OSAS group had statistically significantly lower plasma IL-10 level than females in the same group (p<0.05). There was no statistically significant difference between IL-10 levels of both sexes in the control group (p>0.05) (Table 5).

Linear regression was performed to identify independent factors influencing plasma IL-10 level. Dependent variable was plasma IL-10 level. Independent factors were age, sex, BMI, AHI, time S_{O2}<90%, IL-6, TNF-α, position dependence of apnea. None of the independent factors had significant influence on IL-10 level (p>0.05).

TNF-α

The mean plasma TNF-α levels were 0.50±0.20 pg/ml in the OSAS group and 0.55±0.25pg/ml in the control group. This difference was not statistically significant (Student's test, t=1.02, p=0.31). TNF-α levels of sexes and positional dependence of apnea did not differ significantly (p>0.05) (Table 6).

Linear regression was performed to identify independent factors influencing plasma TNF-α level. Dependent variable was plasma TNF-α level. Independent factors were age, sex, BMI, AHI, time S_{O2}<90%, IL-6, IL-10, position dependence of apnea. Age was determined as the only significant independent factor (t=2.066, p=0.042). TNF-α increased with increasing age.

Correlation analysis

Pearson bivariate correlation analysis was performed between IL-6, IL-10, TNF-α, BMI, AHI, time S_{O2}<90%, age and sex in all patients. There was a positive significant correlation between age and TNF-α (r=0.225; p=0.042), between BMI and AHI (r=0.306, p=0.005), between BMI and time S_{O2}<90% (r=0.426, p<0.001), between AHI and time S_{O2}<90% (r=0.779, p<0.001), and between IL-6 and TNF-α (r=0.224, p=0.043). There was a negative significant correlation between sex and AHI (r= -0.273; p=0.013), indicating males having higher AHI compared to females. The other correlations were not statistically significant (p>0.05).

Table 1: Comparison of OSAS and control groups.

Findings	**OSAS**	**Control**	**Statistics**
N	*42*	40	
Gender(F/M)	12/30	13/27	χ^2=0.15, p=0.70
Age	48.1±11.3	46.2±9.7	t= 0.876,p= 0.643
AHI 0-4.9 5-14.9 15-29.9 >30	24.3±16.2 9 (21.4 %) 14 (33.2 %) 19 (45.2 %)	3.6±1.3 40(100%)	
BMI	30.2 ± 7.8	29.7 ± 4.9	t=1.925, p=0.11
sO_2 <90%	16.3 ± 9.8	3.3 ± 2.8	t=4.769, p=0.003

Table 2: Plasma cytokine concentrations in all patients subdivided by their AHI values (Analysis of variance)

	AHI, events per hour					
	0–4.9	5-14.9	15.0-29.9	≥30.0	F	p
Subjects, N (%)	40 (48)	9 (11)	14 (17)	19 (24)		
IL-6 (pg/dl)	0.92	1.23	3.76	6.99	5.876	0.001
IL-10 (pg/dl)	1.94	1.62	0.98	0.33	3.745	0.002
TNF-α (pg/dl)	0.55	0.41	0.54	0.51	0.836	0.48

Table 3: Cytokine levels according to BMI (Analysis of variance)

Cytokine	BMI Normal (≤25) (N=16)	Overweight (25<BMI≤30) (N=37)	Obese (>30) (N=29)	Statistics
IL-6	2.08	1.91	2.91	F=1.041, p=0.36
IL-10	1.02	0.75	0.85	F=0.492, p=0.61
TNF-α	0.49	0.52	0.55	F=0.334, p=0.72

Table 4: IL- 6 levels and patients' features (Student's t-test)

	IL-6(pg/dl)	t	P
OSAS	4.68±0.24	t= 6.925	p=0.008
Female	1.90±0.13		
Male	5.47±2.81	t=4.786	p=0.003
Control	0.92±0.02	t= 6.925	p=0.008
Female	0.89±0.26		
Male	1.02±0.41	t=0.759	p=0.214
Position dependence			
Non-positional apnea	5.6±1.7		
Positional apnea	0.9±0.3	t=7.565	p=0.001

Table 5: IL- 10 levels and patients' features

	IL-10(pg/dl)		**Statistics**
OSAS	0.82±0.54	t= 2.325	p=0.007
Female	0.90±0.13	t=4.786	p=0.003
Male	0.77±0.11		
Control	1.94±0.73	t= 2.325	p=0.007
Female	1.89±0.19	t=0.364	p=0.817
Male	2.02±0.21		
Position dependence			
Non-positional apnea	0.57±0.27	t=1.112	p=0.273
Positional apnea	0.75±0.69		

Table 6: TNF-α level and patients' characteristics

	TNF-α (pg/dl)	**Statistics**
OSAS	0.50 ± 0.20	t=1.02, p=0.31
Female	0.57 ± 0.20	t=1.45, p=0.156
Male	0.47 ± 0.20	
Control	0.55 ± 0.25	t=1.02, p=0.31
Female	0.547 ± 0.28	t=0.048, p=0.96
Male	0.551 ± 0.23	
Position dependence		
Non-positional apnea	0.51 ± 0.20	t=0.45, p=0.66
Positional apnea	0.48 ± 0.21	

DISCUSSION

OSAS is a chronic and repetitive upper airway collapse during sleep, causing chronic hypoxemia. It could provoke oxidative stress and systemic inflammation. Patients with OSAS have repetitive short cycles of oxygen desaturation in their sleep. This hypoxemia can promote activation of various inflammatory cells, especially lymphocytes and monocytes, which increase the levels of inflammatory factors including TNF-α, IL-6 and decrease anti-inflammatory factors such as IL-10[5].

There is a growing awareness of the role of inflammation as the intermediary mechanism between OSAS and cardiovascular risks in adults and it has been etiologically linked most convincingly to hypertension. Hypertension induced by OSAS may be multifactorial in origin and may include systemic inflammation, oxidative stress, endogenous vasoactive factors, endothelial dysfunction, increased sympathetic activation, and metabolic dysregulation. Systemic inflammation caused by pro-inflammatory cytokines is one of the important consequences[6]. Inflammatory markers, including CRP, TNF-α, IL-6 and IL-8 are elevated and IL-10 is decreased in adults with OSAS and have been associated with increased risk of cardiovascular disease[7]. Xiaoshun Qian et al established that serum TNF-α and IL-6 were higher but IL-10 was lower in OSAS patients with hypertension compared to OSAS patients without hypertension[8]. In our study, we found that plasma IL-6 was significantly higher, IL-10 was significantly lower in the OSAS group compared to control group. TNF-α was not significantly different between OSAS and control group.

Oxidative stress in the form of oxygen and nitrogen radicals leads to tissue damage. Cytokines (IL-6, IL-10, TNF-α, etc.) are responsible for tissue repair and reperfusion. It can be hypothesized that short-lasting but recurrent hypoxemic episodes and reactive oxygen species in OSAS patients can increase the production of pro-inflammatory cytokines by mononuclear cells, as suggested by experimental evidence[9,10]. This may be responsible for the rise in their peripheral blood levels, as a result of the spill-over into the circulation from these cells[10]. In our study, we found that the time at S_{O2} < 90% during total sleep period was significantly higher in OSAS group compared to control group. The prevailing Th1-type cytokine pattern of immune cells in the peripheral blood of OSAS patients can partially be explained by hypoxia. In fact, experimental evidence supports the role of hypoxia in inducing the expression of pro-inflammatory cytokines, in particular TNF-α, but also IL-1b and IL-6[11].

In our study, serum IL-6 levels were significantly higher in the OSAS group compared to the control group. Plasma IL-6 levels increased significantly as the OSAS severity increased. Plasma IL-10 levels decreased significantly as the OSAS severity increased. TNF-α level did not change significantly as the OSAS severity increased. However, multifactorial analysis revealed that TNF-α level determined IL-6 level independently; as TNF-α level increased so did IL-6 level.

IL-6 is a potent pro-inflammatory cytokine characterized by pleiotropy and different physiological and pathological functions involving multiple systems. Plasma levels of IL-6 have been repeatedly found to be increased in patients with OSAS and are reduced after effective CPAP treatment[12]. Vgontzas et al. have shown that IL-6 levels are elevated in experimentally induced sleepiness in healthy young adults after one or several nights of total sleep deprivation or even after partial sleep deprivation for 1 week[12,13]. Administration of etanercept, a TNF-α antagonist, was associated with a significant reduction in IL-6 and in sleepiness. In fact, plasma levels of IL-6 appeared to correlate with daytime sleepiness in OSAS patients and in healthy individuals after sleep deprivation[14]. We also detected that patients with non-positional apnea had significantly higher serum IL-6 levels than those with positional apnea.

The increased production of IL-6 in breath condensate of OSAS patients has been attributed to local adipose tissue, based on the observation of a significant correlation between neck circumference and IL-6 levels[14,15]. Shuo Li et al. found greater circulating levels of IL-6 when rats were exposed to intermittent hypoxia. Intermittent or sustained hypoxia could enhance the production of IL-6. It is also of note that the levels of IL-6 under intermittent hypoxia did not exhibit the biphasic changes shown by other cytokines. This increase might be related to body fat composition. Increased percentage of body fat could therefore contribute to the production of IL-6 in circulation[15]. In another study, Vgontzas et al. found that the concomitant presence of OSAS in obese patients appeared to be associated with the highest levels of IL-6[16]. Although the study above suggested that obesity was a pivotal determinant of the increase of IL-6, in our study we did not find any positive significant correlation between the level of IL-6 and BMI. We found that as the BMI increased

IL-6 level did not change significantly. Therefore, obesity alone was not a significantly important factor in the increase of IL-6.

In our study, serum IL-6 levels were significantly higher in male patients with OSAS compared to female patients with OSAS. This result showed that male patients with OSAS were exposed more to hypoxemia than females with OSAS. In the control group, IL-6 level did not change significantly according to gender.

Another interesting result of our study is that on patients with positional apnea plasma levels of IL-6 (0.9±0.3) were significantly lower than that (5.6±1.7) of those with non-positional apnea. Whether IL-6 levels could be used to predict this type of sleep disorder is unknown and should be determined by further studies.

IL-6 levels in patients with OSAS higher than levels in controls and there is a positive relationship between previously pro-inflammatory cytokines' levels and AHI, which reflects the severity of OSAS. We concluded that sleep apnea contributes to the cytokine elevation and speculated that this elevation might play a role in the increased frequency of cardiovascular complications associated with OSAS.

Based on our findings, it can be hypothesized that increased levels of IL-6 and decreased levels of IL-10 in OSAS patients contributed to sleep apnea. By inducing sleepiness, which is associated with more apnea, increased levels of IL-6 and decreased levels of IL-10 would establish a vicious cycle in the pathogenesis of OSAS. We must also consider the gender when planning treatment of OSAS. Because female patients appear to be less likely to be effected by inflammation than male patients.

The functional roles of TNF-α in the modulation of physiological sleep have been studied and suggest a potent somnogenic effect for this cytokine via its cognate receptor. TNF-α is also a major cytokine having a role in development of inflammation. The presence of systemic inflammation, characterized by elevated levels of certain potent pro-inflammatory mediators, such as C-reactive protein, leptin, TNF-α, IL-1ß, IL-6, reactive oxygen species and adhesion molecules, may predispose to the development of cardiovascular complications observed in patients with OSAS. TNF-α may stimulate the production of endothelin-1 and angiotensinogen. Serum TNF-α concentration has been reported to be positively correlated with systolic blood pressure and insulin resistance in humans and increased TNF-α secretion has been observed in monocytes in hypertensive patients[17].

Medical literature includes many studies about TNF-α and its pro-inflammatory effect. High serum level of TNF-α has a role in the development of inflammation and many systemic diseases. Studies also show a relation between TNF-α and OSAS. Kataoka et al found that serum TNF-α levels in patients with OSAS were significantly elevated in comparison to normal healthy subjects. They also found that the surgical treatment of OSA patients reduces the serum TNF-α levels[18]. Our results indicated that plasma TNF-α level did not differ significantly between OSAS and control groups and that TNF-α level did not change significantly as OSAS severity increased. TNF-α level was independently determined by patient's age only. According to our results TNF-α does not appear to play a significant role in OSAS.

IL-10 is a pleiotropic cytokine and inhibits a broad array of pro-inflammatory immune responses. IL-10 expression was negatively correlated with the severity of OSAS[19]. Alberti et al found that there was a significant decrease in the peripheral plasma levels of IL-10 in patients with OSAS[20]. We also detected significantly lower serum IL-10 levels in patients with OSAS compared to controls. Plasma IL-10 level decreased significantly as OSAS severity increased.

In this study, we observed a significant increase in the plasma levels of the proinflammatory cytokine IL-6 in our OSAS patients, but not TNF-α. A significant decrease in the peripheral plasma levels of IL-10 was also found in our OSAS patients compared to the control group. Increased release of TNF-α and IL-6 and decreased release of IL-10 may have a role in the development of inflammation which may give rise to systemic diseases. These findings support a systemic activation of the inflammatory response in OSAS patients, which also appears to be associated with its severity and duration, sleep efficiency, AHI, and percentage of time with apnea and hypopnea.

The strong association of IL-6 and IL-10 with AHI also suggests that they may be used for monitoring the progress of OSAS treatment. These biomarker assays may also be used in fieldwork if a portable sample collector is developed. Thus, its role in public health surveys and OSAS control programs, such as screening of drivers and hypertension patients, should not be underestimated.

SONUÇ

Patients with OSAS have increased circulating levels of IL-6 and decreased circulating

levels of IL-10. TNF-α does not appear to play a significant role in OSAS. The increase in pro-inflammatory cytokine, IL-6, production and decrease in anti-inflammatory cytokine, IL-10, production in OSAS patients may have important health consequences. Therefore, we suggest that these two cytokines be measured in blood of patients with OSAS, especially in males, before planning treatment because they give information about the systemic damage imposed by OSAS. Future studies are necessary to determine their role in the development of OSAS complications.

Conflict of interest: We have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus;membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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