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Inflammatory Cytokine Level in Patients with Obstructive Sleep Apnea and Treatment Outcome of Oral Appliance Therapy

Jae-Tak Oh, Jin-Woo Chung

Department of Oral Medicine and Oral Diagnosis, School of Dentistry and Dental Research Institute, Seoul National University, Seoul, Korea

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Correspondence to:
Jin-Woo Chung
Department of Oral Medicine and Oral Diagnosis, School of Dentistry, Seoul National University, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-2072-3021
E-mail: jwchung@snu.ac.kr

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Purpose: The aims of this study were to analyze the association between inflammatory cytokine and obstructive sleep apnea (OSA), and to evaluate treatment outcome and changes of plasma inflammatory cytokine levels after oral appliance therapy.

Methods: Twenty-seven subjects who visited Department of Oral Medicine in Seoul National University Dental Hospital were performed nocturnal polysomnography and analyzed plasma C-reactive protein (CRP), interleukin (IL)-1β, IL-6, IL-10, and tumor necrosis factor (TNF)-α levels. Each subject was evaluated with Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS). The subjects were classified into 12 OSA patients (apnea-hypopnea index [AHI] >5) and 15 control (AHI ≤5) groups. The OSA group was treated with mandibular advancement device (MAD) for 3 months and re-evaluated nocturnal polysomnography and plasma inflammatory cytokine levels.

Results: Plasma TNF-α, IL-10, and IL-6 levels were significantly higher in OSA patients compared to controls. Total AHI showed significant positive correlations with plasma IL-6 and TNF-α levels. Percentage time of SpO_2 <90 and lowest SpO_2 were significantly correlated with plasma TNF-α level. ESS showed significant positive correlation with plasma IL-10 level. Total AHI, percentage time of SpO_2 <90, lowest SpO_2, and mean SpO_2 were significantly improved after the MAD therapy. Plasma TNF-α level was significantly decreased after MAD therapy.

Conclusions: We suggest that MAD therapy is an effective treatment modality for patients with OSA and can decrease plasma cytokine level.

Key Words: C-reactive protein; Interleukins; Mandibular advancement device; Obstructive sleep apnea; Tumor necrosis factor-α

INTRODUCTION

Inflammatory cytokines are various intercellular signaling proteins which are involved in the regulation of local and systemic inflammatory responses. They carry out many important functions in biological processes by binding to specific surface receptors of target cells.[1] Inflammatory cytokines are produced in peripheral lymphocytes, macrophages, and somatic cells and are not produced in specific glands unlike endocrine hormones. Most cytokines act in autocrine or paracrine fashion, so only small amounts are detected in the blood of healthy individuals.

Inflammatory cytokines were generally known to exist in the peripheral immune systems, but recently cytokines and their receptors have also been found in the brain, and have been discovered to be produced in the neurons and glial cells. It is known that cytokines take part in central nervous system processes including the regulation of arousal state, modulation of mood, feeding, thermoregulation, and sexual behavior, so they are considered as mobile brain.

Sleep regulation is one of the multiple functions of inflammatory cytokines. During the past two decades of studies, it has been reported that interleukin (IL)-1β, tumor necrosis factor-α (TNF-α), and IL-6 are strongly involved in physiologic sleep regulation without stimuli causing immune responses.[2]

Sleep is not a passive state of reduced neuronal cell activity, but an active process of diverse recovery processes for an individual's health. Sleep deprivation not only causes excessive daytime sleepiness but also increases the risk of weight gain, diabetes, cardiovascular disease, and hypertension. An absolute lack of sleep or low quality of sleep cause body changes such as general fatigue and sleepiness, and changes in the secretion of inflammatory cytokines. Reversely, changes in inflammatory cytokines secretion also affect sleep quality.[3,4]

Snoring is a common symptom affecting about 20% of adult men over 40 years old. Snoring is the noise caused by vibration of the pharyngeal wall and surrounding soft tissue during respiration, and causes repeated partial or complete closure of the upper airway during sleep. When the upper airway is closed partially or completely during sleep, the patient's lung cannot be supplied with air, and this is called obstructive sleep apnea (OSA). These sleep-related breathing disorders cause serious health problem.[5-10]

The symptoms of OSA are frequent awakenings and repeated hypoxia during sleep. The patients with OSA complain of daytime sleepiness, fatigue, feeling of not being refreshed in the morning, and cognitive functional disorder. Most patients usually want to be treated because of their social problems caused from severe snoring, but sleep apnea and associated problems should be the major cause of treatment. Habitual and chronic primary snoring only reflects mild sleep disorder which does not threaten health, but sleep apnea can be a risk factor of physiologically important diseases such as hypertension, heart failure, and stroke. According to a previous epidemiological study, the cumulative survival rate of OSA patients with an apnea-hypopnea index (AHI) over 20 is about 70% of that of patients with an AHI under 20.

Etiological factors of OSA are obesity, maxillofacial deformity such as mandibular retrognathism and micrognathia, large tongue and large tonsil. Age is also correlated with the prevalence of OSA. The airflow via the upper respiratory airway during sleep is related to the size and stiffness of the upper respiratory tract, and the neuronal control of pharyngeal muscles. In recent studies, a strong association between inflammatory cytokines and OSA has been reported as we have mentioned above.[11,12]

For mild OSA, lifestyle changes such as sleep posture change, weight control, cessation of alcohol, and regular exercises can be a therapeutic option, but in severe OSA these may not be effective. For the treatment of moderate to severe OSA, pharyngeal or orthognathic surgeries, and continuous positive airway pressure (CPAP) have been suggested. Recently, many oral appliances have been developed and effectively used in dental clinics for the treatment of OSA because these treatment modalities are reversible and relatively simple.

There are several studies reporting on the changes of inflammatory cytokines after CPAP and pharyngeal surgery, but we could not find a study on the changes of plasma cytokine levels after oral appliance treatment.

The aims of this study were to analyze the association between inflammatory cytokine and OSA, and to evaluate treatment outcome and changes of plasma inflammatory cytokine levels after oral appliance therapy.

MATERIALS AND METHODS

1. Subjects

Twenty-seven subjects who visited the Snoring and Sleep Apnea Clinic of the Department of Oral Medicine, Seoul National University Dental Hospital (Seoul, Korea) were examined by nocturnal polysomnography and their serum inflammatory cytokine levels were analyzed.

The subjects were classified into 12 OSA patient (AHI >5) and 15 control (AHI ≤5) groups according to the polysomnography results. The OSA group was treated with mandibular advancement device (MAD) for 3 months and re-evaluated nocturnal polysomnography and plasma inflammatory cytokine levels. Exclusion criteria of the subject were infection, injury, or surgical operation within 6 months; collagen, hematological, allergic, cardiovascular, respiratory, or malignant disease; and any medication affecting plasma cytokine level within 1 month before the baseline

examination.

The study was approved by the Institutional Review Board of Seoul National University Dental Hospital (IRB no. CRI 11033).

2. Evaluation of Sleep Quality

Sleep quality was evaluated by means of the Pittsburgh Sleep Quality Index (PSQI) and daytime sleepiness by means of the Epworth Sleepiness Scale (ESS). Subjects with a PSQI score of more than 6 are considered to have poor-quality sleep and those with an ESS score of more than 10 to suffer of excessive daytime sleepiness.

3. Polysomnography

Multi-channel recordings of electroencephalogram (EEG), submental and leg electromyogram (EMG), electrocardiogram (ECG), nasal thermistor, nasal pressure transducer, thoracic and abdominal piezoelectric belts, and oxygen saturation were performed using level I polysomnography (Alice 5; Respironics, Pittsburgh, PA, USA). Body position was also confirmed through direct observation of the patient by the technician using a low light camera and simultaneous digital recording with a posture tag at the thoracic piezoelectric belt.

Sleep was staged and respiratory events were scored using the standard criteria of the American Academy of Sleep Medicine. Briefly, OSA was defined as a reduction in airflow greater than 90% with a duration of at least 10 seconds in which there was persistent respiratory effect, whereas hypopnea was defined as a reduction of airflow by 30% for more than 10 seconds accompanied by oxygen desaturation ≥3%.

4. Collection of Plasma

Plasma samples of all controls and patients were obtained from the antecubital vein and stored in Lavender tubes coated with ethylene diamine tetra acetic acid (Becton Dickinson Vacutainer System, Rutherford, NJ, USA). All samples were collected between 9:00 a.m. and 12:00 noon. The plasma was immediately centrifuged (2,000 rpm) for 10 minutes at 4°C, and stored at −70°C before analysis.

5. Quantification of CRP and Inflammatory Cytokines

The plasma concentrations of pro-inflammatory cytokines IL-1β, IL-6, TNF-α, and the anti-inflammatory cytokine IL-10 were measured by means of the Procarta cytokine assays (Panomics, Fermont, CA, USA). The assays are multiplex immunoassays based on xMAP technology (Luminex, Austin, TX, USA). Each cytokine-specific antibody was coupled to a different microsphere labeled with a unique fluorescent dye through covalent bonding. All specimens were incubated in a 96-well microtiter filter plate with the microspheres at 500 rpm for 60 minutes at room temperature. After washing with assay wash buffer, diluted biotinylated secondary antibody was added then incubated at 500 rpm for 30 minutes. Following washing, streptavidin-phycoerythrin was added and incubated for 30 minutes. After another washing, the plate was evaluated with Bio-Plex 200 analyzer (BIO-RAD Laboratories Inc., Hercules, CA, USA) to decide the concentration of the cytokines. Plasma samples were diluted 3-fold with assay diluents. In each plate, the standards and a quality control pool were tested in triplicate, and the 60 samples were tested in duplicate.

Plasma concentrations of CRP were analyzed by means of a highly sensitive immunoturbidimetric assay autoanalyzer (Hitachi 7180; Hitachi High-Technologies Corp., Tokyo, Japan).

The person conducting the measurements was blind to the identity of the subjects.

6. Mandibular Advancement Devices

All appliances used to advance the mandible and were custom made. The SNU appliance was used in this study. The appliances were made by the respective laboratories and the degree of mandibular advancement was set to 60% of the patient's maximum protrusion at the time the impressions were made. For titration, incremental anterior adjustments of the mandible were made until the maximum comfortable limit was reached. An additional sleep study was performed with the MAD after 3 months' of oral appliance therapy to determine treatment efficacy.

7. Statistical Analysis

Comparison of all measures of apnea severity and the effect of MAD between the control and OSA group was

performed by t-test. The relationships between polysomnography parameters and plasma cytokine were evaluated using Pearson's correlation test.

The effect of 3-month treatment of MAD on polysomnography parameters and plasma cytokine levels were evaluated using paired t-test.

RESULTS

1. Subject

Anthropometric features, total AHI, PSQI, and ESS of the two groups are shown in Table 1. Comparing OSA patients and control groups, there were no significant differences in age, body mass index (BMI), PSQI, and ESS scores. There were significant differences in total AHI between two groups.

2. Baseline Plasma Cytokine Levels

Baseline levels of plasma cytokine of the OSA and control group are shown in Table 2. There were significant differences in plasma TNF-α, IL-10, and IL-6 levels between OSA and control groups. Plasma TNF-α, IL-6, and IL-10 levels were higher in OSA patients than controls. There were no significant differences in plasma CRP and IL-1β levels between the two groups.

3. Plasma Cytokines Levels and Sleep Parameters

Spearman's correlation coefficients among plasma levels of CRP, IL-1β, IL-6, IL-10, TNF-α, and sleep parameters are shown in Table 3. There were no significant correlations among PSQI, BMI, and plasma cytokines levels. Total AHI showed significant positive correlations with plasma IL-6 and TNF-α levels ($p<0.01$). Percentage time of SpO_2 <90 showed significant positive correlation with plasma TNF-α level ($p<0.05$). Lowest SpO_2 showed negative correlation with plasma TNF-α level ($p<0.05$). ESS showed significant positive correlation with plasma IL-10 level ($p<0.01$).

4. Sleep Parameters Changes after MAD Treatment

Table 4 shows the changes of sleep parameter after 3

Table 1. Characteristics of the study population

Characteristic	OSA	Control	p-value
Age (y)	41.3±3.0	40.8±3.6	0.729
BMI (kg/m^2)	25.9±3.9	24.8±1.5	0.376
Total AHI	25.89±31.95	1.59±1.19	0.023
PSQI	6.55±3.14	5.07±2.69	0.223
ESS	8.42±4.31	5.60±2.26	0.058

OSA, obstructive sleep apnea; BMI, body mass index; AHI, apnea-hypopnea index; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale.
Values are presented as mean±standard deviation.
p-values were obtained from independent t-test.

Table 2. Comparisons of plasma cytokine levels between OSA and control groups

	OSA	Control	p-value
CRP (mg/dL)	0.11±0.03	0.05±0.01	0.217
IL-1β (pg/mL)	0.66±0.14	0.45±0.03	0.126
IL-6 (pg/mL)	2.76±0.70	0.64±0.17	0.012
IL-10 (pg/mL)	4.65±1.41	1.51±0.23	0.019
TNF-α (pg/mL)	81.16±61.69	3.21±1.12	0.000

OSA, obstructive sleep apnea; CRP, C-reactive protein; IL, interleukin; TNF-α, tumor necrosis factor-α.
Values are presented as mean±standard error of the mean.
p-values were obtained from Kruskal-Wallis test.

Table 3. Correlations among plasma levels of inflammatory cytokines and sleep parameters

Sleep parameter	CRP	IL-1β	IL-6	IL-10	TNF-α
Total AHI	0.130	0.038	0.541**	0.373	0.560**
SpO_2 <90	0.151	0.175	0.355	0.135	0.450*
Lowest SpO_2	−0.167	−0.256	−0.355	−0.160	−0.420*
Mean SpO_2	−0.274	0.072	−0.044	−0.211	−0.135
ESS	0.051	0.014	0.117	0.487**	0.112
PSQI	0.134	−0.231	−0.316	−0.217	−0.030
BMI	0.021	−0.330	−0.263	−0.294	−0.266

CRP, C-reactive protein; IL, interleukin; TNF-α, tumor necrosis factor-α; AHI, apnea-hypopnea index; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; BMI, body mass index.
The appearing values are correlation coefficients of Spearman's correlation analysis.
*Correlation is significant at the 0.05 level. **Correlation is significant at the 0.01 level.

Table 4. Changes of sleep parameters after MAD therapy

Sleep parameter	Baseline	After MAD therapy	p-value
Total AHI (event/h)	25.95±9.22	13.87±9.34	0.007
SpO_2 <90 (%)	3.15±1.62	1.44±1.42	0.027
Lowest SpO_2 (%)	83.42±1.51	90.08±1.31	0.002
Mean SpO_2 (%)	95.17±0.41	96.83±0.41	0.001
ESS	8.64±1.34	6.91±1.30	0.197
PSQI	6.70±1.03	5.40±1.24	0.152

MAD, mandibular advancement device; AHI, apnea-hypopnea index; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index.
Values are presented as mean±standard error of the mean.
p-values were obtained from paired t-test.

Table 5. Changes of plasma cytokine levels after MAD therapy

Cytokine level	Baseline	After MAD therapy	p-value
CRP (mg/dL)	0.11±0.03	0.10±0.03	0.766
IL-1β (pg/mL)	0.66±0.14	0.63±0.09	0.480
IL-6 (pg/mL)	2.76±0.70	3.68±2.94	0.099
IL-10 (pg/mL)	4.65±1.41	4.06±1.80	0.937
TNF-α (pg/mL)	81.16±61.69	8.18±3.81	0.002

MAD, mandibular advancement device; CRP, C-reactive protein; IL, interleukin; TNF-α, tumor necrosis factor-α.
Values are presented as mean±standard error of the mean.
p-values were obtained from Wilcoxon Rank Sum test.

months of MAD therapy. Total AHI ($p<0.01$), percentage time of SpO_2 <90 ($p<0.05$), lowest SpO_2 ($p<0.01$), and mean SpO_2 ($p<0.01$) were improved significantly after 3-month MAD therapy. But ESS and PSQI scores were not significantly changed.

5. Plasma Cytokine Levels Changes after MAD Treatment

Table 5 shows the changes of plasma cytokine levels after 3-months' MAD therapy. There were no significant differences in levels of plasma CRP, IL-1β, IL-6, and IL-10 between baseline and after treatment. Plasma TNF-α level showed significant decrease after MAD treatment ($p<0.01$).

DISCUSSION

The pathogenesis of OSA complications is multifactorial, including systemic inflammation, oxidative stress, and metabolic perturbations. OSA treatment is maintaining airway patency during sleep through CPAP, oral appliance, surgery, and weight loss. Although considerable progress has been made, results are not always certain and long term follow-up is required. So, the usefulness of new biomarkers would be important.

In the present study, AHI index was dropped significantly after MAD therapy. Assessment of AHI index is one of the most generally used criteria evaluating the effectiveness of MAD therapy. Mandibular advancement is directly associated with the efficacy of MAD. Further improvement in inflammatory cytokine levels could also be related to the efficacy of treatment.

We observed that CRP and IL-1β were not significantly different between the OSA and control group, while IL-6, IL-10, and TNF-α were higher in OSA group. Our study demonstrated that TNF-α level, one of the known pro-inflammatory cytokines, increased significantly in patients with OSA than in normal subjects. This finding was in line with the result reported by Vgontzas et al.[13] Other pro-inflammatory cytokines such as IL-1β, IL-6, and CRP have been reported to increase in patients with OSA in comparison with normal subjects.[14,15] But our study did not show the same results in CRP and IL-1β levels. Our study confirmed the fact that plasma IL-6, IL-10, and TNF-α levels are significantly higher in patients with OSA than the control group.[15,16] Plasma CRP and IL-1β levels were not different between the two groups. In some studies CRP and IL-6 levels are elevated in OSA patients compared to the normal group. It has been suggested that elevated CRP level in OSA patients may be related to obesity.[17,18] IL-6 level appears to be predictive of future cardiovascular disease and is elevated in patients with unstable angina compared to those with stable angina. Elevated IL-6 level is often found to correlate with CRP levels.[18]

IL-1β is a marker of systemic inflammation and activated innate immunity, and has been reported to be elevated in OSA patients.[19] In our study IL-1β level was higher in the OSA group than in the control group, but no significant difference was found.

We also observed increased IL-10, an anti-inflammatory cytokine, in OSA patients, which is an identical same result reported by Sahlman et al.[20] This finding might represent a compensatory mechanism aiming to reduce the inflammatory response. IL-10 level after 3-months' MAD therapy was slightly decreased but it was not significant. This result

should be further studied.

In our study total AHI showed significant positive correlations with plasma IL-6 and TNF-α levels. SpO_2 <90, and lowest SpO_2 showed significant correlations with plasma TNF-α levels. These results speculate that hypoxic damage can induce general inflammatory condition by increasing inflammatory plasma cytokines. OSA represents intermittent hypoxemia during sleep and these conditions can be the predisposing factors of cardiovascular disease such as pulmonary hypertension, ischemic heart disease, and cardiovascular accident.

Our study showed that an effective treatment with MAD for 3 months in patients with OSA altered plasma TNF-α inflammatory cytokine levels. But other plasma inflammatory cytokines levels such as IL-1β, IL-6, IL-10, and CRP were not improved within 3 months after MAD therapy. These results are similar with a previous research of CPAP therapy.[21] And another research reported that TNF-α and IL-6 levels were decreased in OSA patient after surgical treatment and IL-6 level showed more improvement than TNF-α.[22] We thought longer period of studies and a larger sample size are needed to evaluate the changes of other inflammatory cytokines after oral appliance therapy. For example IL-10 is a cytokine with anti-inflammatory properties capable of modulating inflammatory responses by suppressing the production of pro-inflammatory cytokines such as IL-1β, TNF-α, IL-6, and IL-8.

Elevated TNF-α level predicts the incidence of cardiovascular event in several conditions like heart failure and acute coronary syndrome. TNF-α level has been shown to be a major predictor of mortality and heart failure in acute myocardial infarction. Increased plasma TNF-α is associated with increased mortality in a wide range of heart failure. The TNF-α level of OSA patient were lower than the TNF-α level of heart failure and ischemic patients, but higher than in normal individuals. OSA is thought to be a strong predisposing factor of heart disease in a view of plasma cytokines. So OSA patients with high levels of TNF-α should be examined and treated for the prevention of heart diseases.

In our studies MAD therapy ameliorated the level of TNF-α after 3-months of follow-up. Circulating levels of TNF-α have been reported to correlate with signs of early atherosclerosis amongst healthy middle-age men and are predictive of coronary heart disease. Moreover persistently increased levels of TNF-α after myocardial infarction are predictive of future coronary events. MAD therapy is a very useful treatment for OSA and would reduce the risk of future cardiovascular problems. MAD therapy has some advantages over CPAP or surgical therapy. The significant decrease of plasma TNF-α level in OSA patients who complied with MAD use could lead us to the argument of the direct effect of OSA on systemic immunity. So it could be said that MAD therapy is a useful treatment for OSA and its general inflammatory sequelae.

There are several limitations to our study. Firstly, our study was based on relatively a small sample size and short duration of observation. Secondly, we did not apply MAD to the control group. Thirdly, we did not consider systemic diseases of the subjects. There is growing evidence that inflammatory cytokines play important roll in the pathophysiology of cardiovascular disease in patients with OSA. Comorbid disease variables should be considered based on a larger size of population and longer duration in future studies to elucidate mechanisms behind the observed changes in inflammatory mediators.

However, our study is the first study to investigate the effect of oral appliance therapy on plasma cytokine levels and showed that MAD can decrease plasma TNF-α level. Our results also showed associations between OSA and plasma inflammatory cytokine levels.

In conclusion, plasma TNF-α, IL-10, and IL-6 levels were higher in OSA patients compared to controls. Total AHI showed significant positive correlations with plasma IL-6 and TNF-α levels. Percentage time of SpO_2 <90 and lowest SpO_2 were significantly associated with plasma TNF-α level. TNF-α level showed significant reduction between baseline and after MAD treatment.

We suggest that MAD therapy is an effective treatment modality for patients with OSA and can decrease plasma cytokine level.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Kapsimalis F, Richardson G, Opp MR, Kryger M. Cytokines and normal sleep. Curr Opin Pulm Med 2005;11:481-484.
2. Krueger MH, Roth T, Dement WC. Principles and practice of sleep medicine. 4th ed. Philadelphia: Elsevier; 2005.
3. Krueger JM, Majde JA. Humoral links between sleep and the immune system: research issues. Ann N Y Acad Sci 2003;992:9-20.
4. Opp MR, Toth LA. Neural-immune interactions in the regulation of sleep. Front Biosci 2003;8:d768-d779.
5. Koskenvuo M, Kaprio J, Partinen M, Langinvainio H, Sarna S, Heikkilä K. Snoring as a risk factor for hypertension and angina pectoris. Lancet 1985;1:893-896.
6. Norton PG, Dunn EV. Snoring as a risk factor for disease: an epidemiological survey. Br Med J (Clin Res Ed) 1985;291:630-632.
7. Koskenvuo M, Kaprio J, Telakivi T, Partinen M, Heikkilä K, Sarna S. Snoring as a risk factor for ischaemic heart disease and stroke in men. Br Med J (Clin Res Ed) 1987;294:16-19.
8. Yamagishi K, Ohira T, Nakano H, et al. Cross-cultural comparison of the sleep-disordered breathing prevalence among Americans and Japanese. Eur Respir J 2010;36:379-384.
9. Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. Proc Am Thorac Soc 2008;5:242-252.
10. Bixler EO, Vgontzas AN, Lin HM, et al. Sleep disordered breathing in children in a general population sample: prevalence and risk factors. Sleep 2009;32:731-736.
11. Ryan S, Taylor CT, McNicholas WT. Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. Circulation 2005;112:2660-2667.
12. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. JAMA 2000;284:3015-3021.
13. Vgontzas AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K, Chrousos GP. Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. J Clin Endocrinol Metab 1997;82:1313-1316.
14. Shamsuzzaman AS, Winnicki M, Lanfranchi P, et al. Elevated C-reactive protein in patients with obstructive sleep apnea. Circulation 2002;105:2462-2464.
15. Yokoe T, Minoguchi K, Matsuo H, et al. Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. Circulation 2003;107:1129-1134.
16. Punjabi NM, Beamer BA. C-reactive protein is associated with sleep disordered breathing independent of adiposity. Sleep 2007;30:29-34.
17. Sharma SK, Mishra HK, Sharma H, et al. Obesity, and not obstructive sleep apnea, is responsible for increased serum hs-CRP levels in patients with sleep-disordered breathing in Delhi. Sleep Med 2008;9:149-156.
18. Ryan S, Nolan GM, Hannigan E, Cunningham S, Taylor C, McNicholas WT. Cardiovascular risk markers in obstructive sleep apnoea syndrome and correlation with obesity. Thorax 2007;62:509-514.
19. Chin K, Ohi M, Kita H, et al. Effects of NCPAP therapy on fibrinogen levels in obstructive sleep apnea syndrome. Am J Respir Crit Care Med 1996;153:1972-1976.
20. Sahlman J, Miettinen K, Peuhkurinen K, et al; Kuopio Sleep Apnoea Group. The activation of the inflammatory cytokines in overweight patients with mild obstructive sleep apnoea. J Sleep Res 2010;19:341-348.
21. Steiropoulos P, Kotsianidis I, Nena E, et al. Long-term effect of continuous positive airway pressure therapy on inflammation markers of patients with obstructive sleep apnea syndrome. Sleep 2009;32:537-543.
22. Constantinidis J, Ereliadis S, Angouridakis N, Konstantinidis I, Vital V, Angouridaki C. Cytokine changes after surgical treatment of obstructive sleep apnoea syndrome. Eur Arch Otorhinolaryngol 2008;265:1275-1279.