The Association between the Levels of Inflammatory Serum Markers and Severity of Obstructive Sleep Apnea

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Abstract

Background and Objective: Higher concentration of systemic inflammatory markers is reported in patients with obstructive sleep apnea (OSA). Levels of inflammatory markers may be associated with severity of OSA. Objective of this study was to evaluate the correlation between level of inflammation markers and OSA severity.

Materials and Methods: Fifty six patients with symptoms and signs of OSA free of prevalent medical conditions including cardiovascular disease, diabetes mellitus, and hypertension were recruited in this study. Full night polysomnography (PSG) was performed for all the study participants. Participants' blood samples were taken to analyze serum concentrations of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in the morning after PSG.

Results: The mean age of participants was 40.32 ± 10.78 years with mean body mass index (BMI) of 28.72 ± 4.96 kg/m^2. 46 participants (82%) were male. Based on Apnea/Hypopnea Index (AHI), 43 participants (76%) had AHI ≥ 5. Significant difference was found between serum CRP levels in patients with and without OSA (P = 0.03). However, no significant association was observed in terms of ESR levels between the study groups. After adjustment for age, BMI, neck circumference, and heart rate, CRP had no significant difference between the two study groups. In linear regression model, only BMI was correlated with CRP.

Conclusion: This study indicated that BMI is an independent risk factor for elevation of CRP in patients with OSA. Further researches are needed to explore the effects of sleep-related hypoxia on inflammatory serum markers.

Keywords: Obstructive sleep apnea; Inflammatory serum markers; Body mass index (BMI)

Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder caused by partial or total obstruction of upper respiratory airway (1-3). The recurrent episodes of apnea or hypopnea in OSA lead to nocturnal hypoxia (4, 5). Several studies report that intermittent nocturnal hypoxia can stimulate inflammatory pathways and lead to cardiovascular disorders (1, 5, 6). There are variable biomarkers like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) as indices of systemic inflammation for prediction of future cardiovascular events (1, 6-9). CRP is a member of the pentraxin protein family and is an important marker of endothelial dysfunction in the pathogenesis of cardiovascular diseases (10).

CRP is reported to be elevated in patients with OSA (4, 11-14) and may be related to the severity of the syndrome based on the Apnea/Hypopnea Index (AHI) (4, 12, 13).

OSA is very common in obese subjects. Obesity is suggested to be a pro-inflammatory state; so it is difficult to dissociate the role of obesity from the OSA (1, 15, 16).

Some studies believe that there is correlation

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between CRP levels and AHI in patients with OSA (17, 12). In present study, we evaluated the association between OSA and serum inflammatory markers (CRP and ESR).

Materials and Methods

In this cross-sectional study, 56 consecutive subjects were selected based on study inclusion criteria from June 2013 to 2014. Inclusion criteria were as history of sleep disorders except narcolepsy, periodic leg movement syndrome (PLMS), and central apnea.

Exclusion criteria included the history of infectious upper airway disorders, acute or chronic infection, cerebrovascular or cardiovascular events, upper airway surgery, hypertension, diabetes mellitus, hyperlipidemia, alcohol consumption, autoimmune or endocrine dysfunction, malignancy, asthma and other pulmonary disorders.

Written consent form was obtained from each study participant. The study was approved in Ethics Committee of Tehran University of Medical Sciences, Iran.

At first, all of inclusion criteria were evaluated by means of face-to-face interview considering OSA symptoms. Then, participants were asked to complete two validated questionnaires for sleep disorders including Epworth Sleepiness Scale (ESS) and STOP-BANG (Snoring, Tiredness, Observed apnea, Blood Pressure, Body Mass Index, Age, Neck circumference, Gender) questionnaire (18). All the subjects underwent polysomnography (PSG). Demographic characteristics including age, sex, level of education, history of smoking, and alcohol consumption were asked. Body mass index (BMI) (kg/m^2), neck circumference (cm), blood pressure (mmHg) and heart rate (beat/minute) were measured. In the morning after PSG, inflammation markers (CRP and ESR) were measured.

OSA was diagnosed with a full-night PSG evaluating physiological and respiratory variables; apnea and hypopnea were scored using American Academy of Sleep Medicine guidelines (AASM) (19). After PSG reporting, participants were divided into two groups based on their AHI (those with AHI $\geq$ 5 was categorized into OSA group and the ones with AHI < 5 into Non-OSA group.

PSG Measurement

Study participants underwent full-night PSG (Sandman computerized sleep system). The following variables were systematically monitored, electroencephalogram (EEG) (C_3/A_2, C_4/A_1, O_1/A_2,

and O_2/A_1), body position, electrooculogram (EOG), and chin and leg electromyogram. Respiration was monitored using nasal cannula pressure transducer system, mouth thermistor, respiratory plethysmography and pulse oxymetry. PSG was performed with video monitoring and taping. Then, variables were analyzed based on recommendations of AASM guidelines (19).

Measurement of CRP and ESR

Venous blood sample was collected just after awakening and processed within the next 60 minutes. Finally, the patients were divided into two groups based on PSG results, patients with OSA (AHI $\geq$ 5) and the ones without OSA (AHI < 5). The apnea severity measures included AHI, an index of apnea and hypopnea per hour of sleep. AHI < 5 was considered normal, 5-14 as mild OSA, 15-29 as moderate, and $\geq$ 30 as severe OSA.

Metabolic factors [fasting blood sugar (FBS), triglyceride (TG), cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL)], and thyroid hormones were assessed via blood sampling to rule out study exclusion criteria.

Statistical analysis

We used t and chi-square tests for the analysis of dependent variables and evaluation of demographic characteristics between the two study groups. Besides, analysis of variance (ANOVA) was performed for comparisons of dependent variables between the patients with OSA based on severity of disease.

We used linear regression analysis for evaluation of confounding factors.

Except CRP levels, all of the dependent variables had normal distribution. Thus, we used log of CRP levels instead of CRP levels. SPSS software version 17 (SPSS Inc., Chicago, IL, United States) was used for data analysis. P value > 0.05 was considered as statistically significant.

Results

The study sample consisted of 56 participants with mean age of 40.32 $\pm$ 10.78 years and mean BMI of 28.72 $\pm$ 4.96 kg/m^2. Of 56 subjects, 46 (82.14%) were male. Table 1 shows demographic characteristics of the study groups.

Mean serum CRP and ESR levels were normal in all subjects (6.55 $\pm$ 8.73 mg/dl, and 9.40 $\pm$ 7.96, respectively).

Table 1 shows the demographic characteristics of study participants.

Table 1. Demographic characteristics of study participants

Variable		Group [Mean ± SD]		P value
		OSA	Non-OSA	
Age (Year)		41.09 ± 1.74	37.76 ± 2.27	0.330
BMI (kg/m^2)		29.95 ± 4.77	24.95 ± 3.51	0.001
Neck circumference (cm)		40.04 ± 3.10	36.83 ± 3.12	0.030
		n (%)	**n (%)**	
Sex	Male	38 (88)	8 (62)	0.001
	Female	5 (12)	5 (38)	
Smoking+		20 (83.3)	4 (16.7)	0.350

OSA: Obstructive sleep apnea; BMI: Body mass index
n = 43 for OSA and n= 13 for Non-OSA group.

Table 2 compares PSG variables between the case and control groups. There were no significant differences in terms of polysomnographic variables between the two groups except the minimum oxygen saturation rate (%) during total sleep time.

Table 2. Polysomnography variables of study participants

Variable	Group [Mean ± SD]		P value
	OSA	Non-OSA	
Mean of SaO$_2$ (%)	92.13 ± 3.84	93.86 ± 2.01	0.120
Minimum of SaO$_2$ (%)	77.44 ± 1.06	88.5 ± 3.2	0.001
SE	78.40 ± 1.35	73.00 ± 16.53	0.230
Time SaO$_2$ < 90%	16.80 ± 26.1	5.46 ± 15.7	0.143
TST	412 ± 82	401 ± 108	0.680

OSA: Obstructive sleep apnea; SaO2: Oxygen saturation; SE: Sleep efficiency; TST: Total sleep time
n = 43 for OSA and n= 13 for Non-OSA group.

Serum CRP levels were significantly higher in patients with OSA vs. the ones without OSA (P < 0.05). No significant correlation was observed in terms of ESR levels between the two study groups (Table 3).

Table 3 shows serum levels of ESR and CRP in study groups based on severity of OSA.

Table 3. Mean of CRP and ESR in normal subjects and patients with mild, moderate, and severe OSA

Variable	Mean of CRP	Mean of ESR
Non OSA	0.33 ± 0.52	10.38 ± 5.62
Mild OSA	0.49 ± 0.21	9.66 ± 9.68
Moderate OSA	0.64 ± 0.34	7.66 ± 8.31
Severe OSA	0.69 ± 0.50	9.69 ± 8.80
P value	0.216	0.800

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; OSA: Obstructive sleep apnea

After adjusting confounders in linear regression model, we did not find any statistically significant differences between CRP and OSA based on AHI.

Otherwise, BMI was significantly related to CRP (R^2 = 25%, P = 0.040).

We observed the higher score of STOP and STOP-BANG in patients with OSA.

Discussion

The results of current study showed that serum CRP levels were higher in the patients with severe OSA. After adjustment of confounding factors, only BMI had significant association with serum CRP levels. This finding was similar to studies that showed the serum CRP level is associated with BMI in patients with OSA (4, 20). However, some studies has revealed this association to be BMI-independent (12, 18, 21, 22). It seems that elevation of systemic inflammation markers is present in overweight and obese persons.

Current results showed correlation between OSA severity and CRP levels, but the relationship was not statistically significant. This finding is consistent with Chung et al. study (4). However, some studies have showed significant association between OSA and serum concentration of CRP (12, 13, 17).

BMI may be an important risk factor in elevation of CRP level other than severity of OSA. Thus, it is suggested to conduct further studies among groups with different BMI values to reveal the role of AHI in elevation of serum inflammatory markers.

Along with other reports, current study did not find any significant difference in terms of ESR levels between study groups and also subgroups of patients with OSA.

Serum ESR levels were significantly higher in female patients which may be due to effect of sex on serum ESR level (6, 23). Current study showed that CRP and ESR were not associated with PSG variables, except Minimum SaO$_2$% and high level of CRP (22).

In this study, we observed the higher score of STOP and STOP-BANG in patients with OSA.

STOP-BANG is highly sensitive measure for OSA screening (24) and could be considered as a powerful tool for stratifying patients in the diagnosis of OSA (25).

Scores of ESS was higher in the OSA group consistent with previous studies (22, 26). Daytime napping may be associated with increased CRP levels (27).

Neck circumference was significantly higher in OSA group in current study. Neck circumference

and retroglossal space are reported to have significant correlation with OSA (28, 29). Results showed that BMI was also higher in the OSA patients. Consistent with previous studies, we observed significant association between BMI and severity of OSA based on AHI (26, 30).

Body weight gain accelerates the progression of OSA or increases the severity of disease from moderate to severe (31, 32). Weight loss also is reported to reduce the severity of OSA (33).

Conclusion

In this study, significant increase of serum CRP level with BMI was observed in all patients. Some previous studies also have showed this finding (4, 34, 35). The associations between inflammatory markers and subclinical atherosclerosis may merely reflect the strong associations between BMI and the levels of inflammatory markers (36).

Further studies are needed to explore the role of inflammatory markers in association of progression or severity of OSA disease.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

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