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Assessment of fibrinogen levels in obstructive sleep apnea patients

Hakan Celikhisar[1], Gulay Dasdemir Ilkhan[2]

[1]Izmir Metropolitan Municipality Hospital, Chest Diseases Clinic, Izmir, Turkey
[2]Tire Public Hospital, Chest Diseases Clinic, Izmir, Turkey

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Abstract

Fibrinogen increases in the acute inflammatory response since it is an acute-phase reactant. Fibrinogen was defined as an independent risk factor for cardiovascular diseases. We aimed to assess the alterations in plasma fibrinogen levels in patients with obstructive sleep apnea syndrome (OSAS) by comparing them with the control cases and determine their relationship with polysomnography (PSG) parameters. The study included 125 newly diagnosed patients with moderate to severe OSAS (defined as apnea-hypopnea index [AHI] ≥ 15) and 82 non-apneic control subjects (AHI<5). A full-night polysomnography was performed in all patients. After the sleep study, blood samples were drawn between 8:00 and 9:00 in the morning to measure fibrinogen levels. In OSAS patients, plasma fibrinogen levels were significantly higher than that of the control cases (4.4±0.12 g/L vs. 3.5±0.16 g/L; p:0.025). Positive correlations were reported between plasma fibrinogen levels and Epworth Sleepiness Scale (ESS) scores (r=0.299, p=0.006), age (r=0.327, p=0.003), body mass index (BMI) (r=0.391, p<0.001), average oxygen desaturation (r=0.258, p=0.019), oxygen desaturation index (r=0.279, p=0.009), time at <90% oxygen saturation (r=0.251, p=0.026), and arousal index (r=0.219, p=0.045). There was a negative correlation between plasma fibrinogen levels and the average oxygen saturation during sleep (r=-0.255, p=0.029). Increased ESS and BMI were related to elevated plasma fibrinogen levels, independent of AHI, in multiple regression analysis. Plasma fibrinogen levels are related with BMI and ESS that supports the link between hypoxia and inflammation. We suggest that elevated fibrinogen levels may be an essential factor in the pathogenesis of vascular disease in patients with OSAS.

Keywords: Obstructive sleep apnea syndrome (OSAS), fibrinogen, Epworth Sleepiness Scale (ESS), hypoxia, vascular disease

Introduction

Obstructive sleep apnea syndrome (OSAS) is described by recurrent upper respiratory tract obstruction, causing intermittent arterial oxygen desaturation, and increased respiratory effort during sleep. Widespread local and systemic inflammation is known to an important pathogenic factor in the development of OSAS and related co-morbidities. The autonomic nervous system, hypo-/semi-reoxygenation cycle, inflammation, and coagulation-fibrinolysis imbalance also have a function in the etiology. Among the complications of OSAS complications, most morbidity and mortality are due to vascular complications. This relationship is not surprising, as OSAS is associated with many vascular risk factors such as increased high-density lipoproteins, high C-reactive protein (CRP), augmented leukocyte adhesion factors, high homocysteine, and glucose intolerance [1].

Fibrinogen is a plasma protein produced in the liver. Fibrinogen has an essential role in coagulation, and it increases in infectious and inflammatory conditions since it is an acute-phase protein. A high fibrinogen value is both an indicator of the inflammatory course in atherogenesis and leads to coronary artery disease through thrombus formation [2,3]. In a meta-analysis, there was a strong relationship between fibrinogen levels and stroke, coronary heart disease, and vascular/nonvascular mortality [4]. An increase of 100 mg/dl in fibrinogen levels has been related to an about 2-fold increase in the risk of major cardiovascular disease [5]. The first clear epidemiological data regarding the link between fibrinogen elevation and cardiovascular mortality independent of other risk factors were presented in a study by Maede et al. [6].

Intermittent hypoxia and associated sympathetic activation are the basis of OSAS physiology. Investigating the consequences of sympathetic activation and hypoxia on the hemostatic system is important to understand the role of the hemostatic system in vascular morbidities associated with OSAS. The mechanism responsible for high fibrinogen levels in patients with OSAS is not clear.

***Corresponding Author:** Hakan Celikhisar, Izmir Metropolitan Municipality Hospital, Chest Diseases Clinic, Izmir, Turkey
E-mail: hcelikhisar@gmail.com

In this study, we aimed to compare plasma fibrinogen levels and evaluate their relationship with polysomnography (PSG) parameters in patients newly diagnosed with OSAS and individuals without apnea.

Materials and Methods

The patients evaluated in the sleep laboratory with the complaints of snoring, witnessed apnea, or excessive daytime sleepiness (EDS) were considered in the study group. Patients diagnosed with moderate to severe OSAS according to all-night PSG results (apnea-hypopnea index [AHI] ≥ 15) were incorporated into the study as the OSAS group and patients who were evaluated as simple snoring (AHI<5) were included as the control group. Exclusion criteria included age under 18 years, pregnancy, alcohol or drug abuse, cerebrovascular disease, malignancy, chronic pulmonary disease, psychiatric disease, coagulopathy, thrombocyte dysfunction, infectious disease, current anticoagulant drug use, and high erythrocyte sedimentation rate (ESR) (> 15 mm/h).

Written informed consents were obtained from all participants. Daytime sleepiness was evaluated using the Turkish version of the Epworth Sleepiness Scale (ESS) [7]. Upon presentation to the sleep center, demographic features, comorbidities, medical treatments, and anthropometric data including weight, height, and body mass index ([BMI; kg/m²]) of all patients are recorded. This study was approved by Bezmialem University Non-Interventional Research Ethics Committee and the registration number is 2011-KAEK-25, 2019/04-02. A total of 125 new diagnosed patients who presented to the sleep center of Esrefpasa Metropolitan Municipality Hospital between January 2018 and June 2019 were included in the study.

In our sleep center, all patients are monitored all night by a trained sleep technician using a PSG device. At least 6 hours of PSG records were acquired. PSG was carried out in agreement with the American Academy of Sleep Medicine Classification criteria [8]. Fasting venous blood samples were drawn between 8 and 9 a.m. the morning after PSG recording. Samples were immediately transported to the laboratory and centrifuged at 1500 × g for at least 10 minutes. Plasma samples were stored between 15 and 25°C for a maximum of 8 hours until measurement. Fibrinogen levels were measured in the biochemistry laboratory by the modified Clauss method using the Dade Behring Multifibren U kit. Fibrinogen concentration was determined in citrated plasma samples using a reference range of 1.8 to 3.5 g/L for both sexes.

Statistical analysis

The data was analyzed with the SPSS 23.0 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY) statistical package program. The distribution of the data, whether normal or not, was assessed with the Shapiro–Wilk test. For normally distributed data, in comparisons between the two groups t-test was used. Relationships between the variables were examined with the Pearson correlation coefficient. Pearson chi-square test and Fisher's exact chi-square test were performed to analyze categorical data. Relationships between fibrinogen and BMI, apnea-hypopnea index (AHI), and ESS score were investigated by multiple regression analysis. The significance level was set as $p<0.05$.

Results

The study included 125 newly diagnosed moderate/severe OSAS patients (AHI≥15) and 82 non-apneic (AHI<5) patients. The demographic and clinical features of both groups are summarized in Table 1. No significant differences were determined between OSAS and control groups regarding age, sex, or smoking habit (p=0.268, p=0.129, p=0.235, respectively). The OSAS group had higher BMI and ESS scores (p=0.03, p<0.001, respectively). While hypertension was more common in the OSAS group, the frequencies of diabetes mellitus or coronary artery disease were similar between the two groups.

The polysomnographic features of both groups are summarized in Table 2. The groups differed significantly in time spent in stage 3 sleep, AHI, apnea-hypopnea time, arousal index, sleep time at <90% oxygen saturation, the mean oxygen saturation, and oxygen desaturation index (ODI) 2 and 3 values (p<0.001 for all) (Table 2).

Table 1. Clinical characteristics of OSAS and control group

	OSAS (n=125)	Control (n=82)	p
Age (years), mean±SD	49.60±1.42	47±2.00	0.268
Male/Female (n)	107/18	60/22	0.129
BMI (kg/m2), mean±SD	32.00±0.90	29.20±0.64	0.030
Smoker/Non-smoker (n)	85/40	42/40	0.235
Smoking history (pack-years), mean±SD	15.64±2.19	10.35±2.40	0.124
Coronary artery disease (n)	8/118	10/72	0.420
Hypertension (n)	57/68	15/67	0.009
Diabetes mellitus (n)	20/105	3/79	0.080
Epworth Sleepiness Scale, mean±SD	10.5±0.79	4.7±0.61	<0.001
Fibrinogen (g/L)	4.4±0.12	3.5±0.16	0.025

OSAS: Obstructive sleep apnea syndrome, BMI: Body mass index, SD: Standard deviation

Table 2. Comparison of polysomnographic parameters of OSAS and control group

	OSAS (mean+SD)	Control (mean+SD)	p
Time in Stage 3 (% total sleep time)	7.2±1.04	16.5±1.42	<0.001
Time in REM (rapid eye movements) (% total sleep time)	15.2±1.20	16.5±1.16	0.480
AHI (Apnea hypopnea index)	48.7±3.28	1.3±0.21	<0.001
Apnea-hypopnea time (min)	139.7±11.29	2.1±0.38	<0.001
Arousal index	29±2.06	14.6±1.57	<0.001
Average oxygen saturation during sleep (%)	86.8±1.09	95.1±0.32	<0.001
Average desaturation (%)	9.9±0.66	3.7±0.53	<0.001
Time at < 90% oxygen saturation (min)	82.8±12.93	1±0.55	<0.001
ODI (Oxygen desaturation index) 2	79.2±3.40	26.4±2.82	<0.001
ODI (Oxygen desaturation index) 3	68.1±3.95	11±1.61	<0.001

When compared with the control cases, plasma fibrinogen levels were significantly elevated in the OSAS group (4.4±0.12 g/L vs. 3.5±0.16 g/L; p:0.025). Fibrinogen levels were similar in smokers and non-smokers (p=0.905) and correlated with age (r=0.325, p=0.003), BMI (r=0.391, p<0.001), and ESS score (r=0.299, p=0.006). Fibrinogen levels did not show a significant relationship between and AHI or apnea-hypopnea time (p>0.05).

Plasma fibrinogen levels were positively correlated with the mean oxygen desaturation (r=0.258, p=0.019), ODI2 (r=0.279, p=0.009), ODI3 (r=0.252, p=0.022), time below 90% oxygen saturation (r=0.251, p=0.026), and arousal index (r=0.219, p=0.045) and negatively correlated with mean oxygen saturation while awake (r=-0.231, p=0.037) and during sleep (r=-0.255, p=0.029) (Table 3).

In multiple linear regression analysis, ESS score and BMI were determined to be independent variables associated with fibrinogen levels independent of AHI (Table 4).

Table 3. Correlation between fibrinogen and other variables

Variables	Fibrinogen	
	r	p
Age	0.325	0.003
BMI	0.391	<0.001
ESS	0.299	0.006
Waking oxygen saturation	-0.231	0.037
Sleep oxygen saturation	-0.255	0.029
Average oxygen desaturation	0.258	0.019
Time with oxygen saturation < 90%	0.251	0.026
ODI2	0.279	0.009
ODI3	0.252	0.022
Arousal index	0.219	0.045

ESS: Epstein Sleepiness Scale, BMI: Body mass index, ODI: Oxygen desaturation index

Table 4. The results of multiple linear regression analysis

Variables	β	Standard deviation	p
Constant	1.705	0.631	0.009
BMI (Body mass index)	0.065	0.021	0.003
AHI (Apnea-hypopnea index)	-0.005	0.004	0.31
ESS (Epworth Sleepiness Scale)	0.050	0.024	0.04

Discussion

In this study, plasma fibrinogen levels were determined to be significantly higher in the OSAS group than that of the control group and were positively correlated with ESS score and BMI. Besides, significant positive correlations were present between fibrinogen levels and ODI2, ODI3, average oxygen desaturation, and time below 90% oxygen saturation, while negative correlations were determined between fibrinogen levels and oxygen saturation during sleep and wakefulness. It was determined that ESS score and BMI were associated with fibrinogen levels independent of AHI.

The presence of OSAS is defined as one of the most significant risk factors for cardiovascular disease and systemic hypertension [9,10]. Patients with moderate and severe OSAS were reported to have a higher prevalence of left ventricular hypertrophy and diastolic dysfunction [11,12]. The relationship between OSAS and carotid atherosclerosis, a symptom of generalized atherosclerosis, has also been confirmed [13]. Although McArdle et al. stated that there was no strong relationship between OSAS and transient ischemic attack; in the same study they detected a relationship between high fibrinogen levels and myocardial infarction, smoking history, and transient ischemic attack [14]. The presence of sleep apnea in patients with acute ischemic stroke was independently

associated with increased CRP and fibrinogen levels [15].

Besides sleep fragmentation, sleep deprivation, and metabolic disorders, the typical OSAS pattern of intermittent hypoxia and reoxygenation is a major factor in triggering the inflammatory process. Intermittent hypoxia plays an important role in cardiovascular pathogenesis. Peled et al. identified three inflammatory markers, ESR, CRP, and fibrinogen, in the OSAS group [16]. In that study, erythrocyte adhesion and aggregation were found to be stronger in the OSAS patients than the control cases. It has been suggested that these results may explain cardiovascular morbidity.

In previous studies, inflammatory markers were more strongly related to obesity and EDS than AHI [17,18]. In our study, we also observed that ESS and BMI were related to fibrinogen levels independent of AHI. Obesity, especially visceral adiposity, is related to the chronic low-grade inflammation. In a study of obese women and their first-degree relatives, increased CRP and fibrinogen levels were related to BMI and waist circumference [19]. Besides, in a study on obese patients, higher CRP and fibrinogen values were demonstrated in patients with OSAS compared to non-OSAS patients [20].

EDS has many causes and is a fairly common problem. Bixler et al. determined an EDS prevalence of 8.7%, regardless of gender [28]. The relationship between daytime sleepiness score and apnea severity is quite weak. In previous population-based studies, excessive sleepiness was also observed to be a major complaint in most individuals with OSAS [21,22]. In our study, the ESS score was found to be related to fibrinogen levels independent of AHI.

In OSAS, disorders of the inflammatory process and coagulation profile occur, especially concerning the cytokines and fibrinogen [23]. Studies have demonstrated hypercoagulation in OSAS that results from increased platelet activity, an increase in clotting factors, and deterioration of fibrinolysis [24,25]. The probable mechanism underlying this hypercoagulable state is that repeated apneic events during sleep increase sympathetic nervous system activity, which is explained by an increase in catecholamine levels [26]. The increased risk of thrombosis in OSAS has been proven by demonstrating increased platelet aggregation and activation, elevated fibrinogen levels, and decreased fibrinolytic activity [27,28].

It has been suggested that OSAS may cause elevated plasma fibrinogen levels due to edema and plasma cell infiltration. Soft palate inflammation also augments the upper airway obstruction throughout the sleep [29]. One study showed that the OSAS prevalence was higher in patients with ischemic stroke, and fibrinogen levels were also higher in stroke patients with OSAS. In that study, OSAS was independently associated with high fibrinogen levels. Also, fibrinogen was found to be positively correlated with respiratory distress index (RDI), longest apnea time, and mean oxygen desaturation and negatively correlated with mean minimum oxygen saturation. Wessendorf et al. stated that the mechanism behind the augmented risk of stroke in OSAS may be associated with the fibrinogen levels [30]. Therefore, in our study, patients with a diagnosis or history of stroke were excluded. Nobili et al. detected high levels of fibrinogen in the morning in OSAS patients [31]. In another study, OSAS patients' morning fibrinogen levels were elevated than that of the afternoon values [32]. It was also observed that the high morning fibrinogen level decreased after continuous positive airway pressure (CPAP) treatment. In another study, higher plasma viscosity and fibrinogen levels were determined in the OSAS group without diurnal differences, while no changes were observed in fibrinogen levels with CPAP therapy [33].

In this study, we determined significantly higher fibrinogen values in the OSAS group than that of the control group. Nevertheless, fibrinogen levels after CPAP treatment were not evaluated. In a study of Kaditis et al. in children with sleep-disordered breathing (children with snoring and AHI≥5 and children with snoring and AHI<5), fibrinogen values were reported to be elevated in children with snoring than that of the control group without snoring, but no correlation was detected between fibrinogen values and AHI or other PSG parameters [34]. There was no correlation between AHI and other PSG parameters. In a study conducted in adults, fibrinogen levels were reported to be significantly elevated in OSAS patients than that of the control group, and a negative relationship was shown between fibrinogen and average oxygen saturation. However, contrary to our results, a direct association between AHI and fibrinogen values was detected in that study [35].

The main limitations of this study are that plasma fibrinogen levels were determined only in the morning and were not checked after CPAP treatment.

In conclusion, although there was no significant relationship between AHI and fibrinogen in our study; plasma fibrinogen levels were significantly higher in the OSAS group than the control cases. ESS score and BMI were found to be associated with fibrinogen levels independent of AHI. Besides, the positive correlation between plasma fibrinogen levels and nocturnal desaturation supports the relationship between hypoxia and inflammation. The important point to consider is that fibrinogen may be a vascular risk factor in OSAS. It should be remembered that the augmented risk of cardiovascular morbidities, including coronary artery disease, systemic arterial hypertension, heart failure, and stroke poses a major health burden to patients with OSAS.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
The study has been reviewed and approved by a certified Ethical Committee, including the number of the approval document and the date of the approval. The registration number (Bezmialem University Non-Interventional Research Ethics Comittee): 2011-KAEK-25 2019/02-04.

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