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ORIGINAL ARTICLE

Vascular adhesion molecules in men with obstructive sleep apnea: associations with obesity and metabolic syndrome

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Abstract
Introduction Mechanisms linking obstructive sleep apnea (OSA) to vascular diseases as well as obesity and metabolic syndrome are not clear. The purpose of the study was to evaluate levels of vascular adhesion molecules (soluble vascular cell adhesion molecules-1 (sVCAM-1) and E-selectin) in men with obstructive sleep apnea and control subjects and to determine their relations with obesity and metabolic syndrome.
Methods Men with OSA and controls matched for age were included in the study. Overnight polysomnography was performed. Body mass index (BMI) and all the components of metabolic syndrome were evaluated. Serum levels of sVCAM-1 and E-selectin were measured by enzyme-linked immunosorbent assay. Data presented as median (25th and 75th percentiles).
Results Levels of sVCAM-1 (698.2 (627.6–798.2) vs 565.5 (518.8–678.1)ng/ml, p=0.003) and E-selectin (64.9 (50.1–83.1) vs 49.7 (39.8–59.5)ng/ml, p=0.017) were higher in the OSA group compared to the controls. Half of OSA patients had metabolic syndrome. Serum levels of sVCAM-1 and E-selectin did not differ in OSA patients with and without metabolic syndrome. Concentrations of both vascular adhesion molecules correlated with oxygen desaturation index (ODI), but the relation was no more significant after adjustment for all the components of metabolic syndrome. After adjustment for BMI, sVCAM-1 levels positively correlated with oxygen desaturation index (r=0.331, p=0.009).
Conclusions Serum levels of sVCAM-1 and E-selectin were increased in the OSA patient group compared to the controls. sVCAM-1 showed relation with ODI after adjustment for BMI suggesting that it could contribute to development of cardiovascular consequences in OSA patients.

Keywords Obstructive sleep apnea · Obesity · Metabolic syndrome · Vascular adhesion molecules

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Introduction

In obstructive sleep apnea (OSA), repetitive collapses of upper airways during sleep cause pauses of breathing that are followed by decreased oxygen saturation that result in hypoxia/reoxygenation circles called intermittent hypoxia. Intermittent hypoxia is considered to be analogous to the conditions of ischemia and reperfusion injury but it is not as aggressive as it has been demonstrated in ischemic heart disease [1].

OSA is associated with an increased risk for cardiovascular disease, including coronary artery and cerebrovascular diseases [2–7]. In the recent years, both European and USA guidelines for arterial hypertension management have acknowledged OSA to be a novel, frequent, and modifiable cause of systemic arterial hypertension [8].

OSA is closely related to obesity. Obesity itself is associated with endothelial dysfunction and increased inflammation as well [9]. Co-existence of obesity and OSA interact causing metabolic dysfunction and low-grade systemic inflammation. This leads to endothelial dysfunction, atherosclerosis, and vascular diseases [10].

Endothelial dysfunction is an early indicator of vascular damage. The mechanisms of endothelial dysfunctions in OSA are not completely understood. Various inflammation markers, as C-reactive protein, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), intercellular adhesion molecule-1

(ICAM-1), soluble vascular cell adhesion molecules (sVCAM-1), vascular endothelial growth factor (VEGF), and selectins have been demonstrated to be increased in OSA patients [11–13]. Similar findings are reported in patients with metabolic syndrome or cardiovascular diseases [14, 15]. Adhesion molecules are complex membrane proteins located on the cell surface involved with intercellular binding and communication. Among them, E-selectin and sVCAM-1 are predominantly expressed on the surface of endothelial cells and are proatherogenic. The purpose of the study was to evaluate levels of vascular adhesion molecules (sVCAM-1 and E-selectin) in men with obstructive sleep apnea and control subjects and to determine their relations with obesity and metabolic syndrome.

Materials and methods

Study sample

The study was carried out at the Pulmonology and Immunology Department of Lithuanian University of Health Sciences. It was approved by the Kaunas Regional Biomedical Research Ethics Committee (P1-48/2004, version 4, 2010). All the subjects gave their informed consent prior the study.

Patients complaining of OSA symptoms were examined. Medical history was recorded and physical examination was performed by a respiratory physician. None of the subjects has been previously examined or treated for sleep disorders. Exclusion criteria were any known chronic systemic disease, chronic use of medications, infection occurring during the time of examination, alcohol abuse, and smoking. The exception was made for patients with arterial hypertension. Subject treated with one antihypertensive drug or with detected arterial blood pressure >140/80 mmHg during clinical examination were included in the study and considered to be hypertensive. The control group was formed from men complaining of snoring and to whom OSA was rejected by the whole night polysomnography (PSG), when apnea/hypopnea index (AHI) was <5/hour of sleep.

Techniques

Sleepiness was evaluated using the *Epworth* sleepiness scale (ESS) [16]. Anthropometric measurements such as height, weight, and circumference of waist were taken. Body mass index (BMI) was calculated by dividing weight in kilograms by squared height in meters (kg/m^2).

All the subjects underwent a whole night attended polysomnography (PSG) using a computerized polysomnography system (*Alice 4*, Respironics). The following parameters were documented: sleep stage electroencephalogram (EEG), electrooculogram and chin-miogram, electrocardiogram, airflow, thoracic and abdominal movements, oxygen saturation (SpO_2), body position, leg movements, and snoring. Sleep recordings were scored manually. EEG was scored in 30-s epochs and staged according to the criteria of Rechtshaffen and Kales [17]. An apnea was defined as cessation of breathing for >10 s, a hypopnea—as a reduction of airflow ≥50 % associated with desaturation of ≥3 % or an EEG arousal, both lasting for ≥10 s [18]. An apnea/hypopnea index was calculated as a total number of apneas and hypopneas per hour of sleep. An oxygen desaturation index (ODI) was calculated and defined as a total number of desaturations ≥3 % per hour of sleep. An arousal index (AI) was calculated and defined as a total number of arousals per hour of sleep. Average oxygen saturation during sleep time (average SpO_2), lowest oxygen saturation during sleep time (lowest SpO_2), and percent of total sleep time spent with SpO_2 <90 % (SpO_2 <90 % (TST%)) were evaluated. OSA was defined as AHI ≥5 events per hour of sleep and daytime and nighttime symptoms as suggested in the International Classification of Sleep Disorders by American Academy of Sleep Medicine [19].

Venous blood samples were obtained at 7 a.m. in a fasting state in the morning after the diagnostic PSG. Lipid profile consisting of total cholesterol (TC), high-density lipids (HDL), low-density lipids (LDL), and triglycerides (TG) as well as glucose concentration were measured by standard enzymatic methods for routine estimation. Samples obtained into serum vacutainers were centrifuged and separated serum was stored frozen at −70 °C until examination. Serum adhesion molecules, i.e., sVCAM-1 and E-selectin, were measured by enzyme-linked immunosorbent assay (ELISA) method using standard kits (IBL International, GmbH, Hamburg, Germany). All measurements were duplicated.

All the subjects were evaluated for the prevalence of separate components of metabolic syndrome and metabolic score was calculated (metabolic syndrome: adult treatment panel definition III: presence or absence of arterial hypertension, waist circumference >102 cm in men, TG≥1.7 mmol/l, HDL <1.03 mmol/l, glucose≥5.6 mmol/l) [20].

Statistical analysis

Statistical analysis was performed using standard statistical software package *SPSS 18.0* (SPSS Inc. Chicago, IL). Descriptive results for continuous variables are presented as median and 25th and 75th percentiles. Comparison between OSA patient and control groups was established using Mann–Whitney *U* test. χ^2 was used for detecting differences in categorical data. Bivariate correlations were calculated using *Spearman's* coefficient. For partial correlation analysis not normally distributed variables were transformed logarithmically (*ln*). A p value<0.05 was considered to be statistically significant.

Results

A total number of 65 patients with OSA and 13 controls were included in the study. Characteristics of the two groups are presented in Table 1. The two groups were age matched. ESS results did not differ between the two groups. The OSA group differed from the controls in terms of all polysomnographic and anthropometric parameters. Blood TG and glucose levels were lower in the control group. Only one control subject met diagnostic criterion of the component of metabolic syndrome according to the TG levels. As it is known that metabolic syndrome as well as obesity could act as confounding factors influencing serum levels of vascular adhesion molecules, all the subjects were evaluated regarding metabolic syndrome. Comparison of the prevalence of different components of metabolic syndrome and metabolic score are presented in Table 2. In the OSA patients group, 34 patients had metabolic syndrome. Serum levels of sVCAM-1 and E-selectin did not differ in OSA patients with and without metabolic syndrome.

As expected, sVCAM-1 and E-selectin concentrations were higher in OSA patients compared to the controls (Table 1). Correlations between vascular adhesion molecules and anthropometric and polysomnographic measures in patients with OSA are shown in Table 3. No significant relation was detected between levels of vascular adhesion molecules and any parameter of lipid profile or glucose levels.

sVCAM-1 levels showed significant correlations with AHI, AI, and ODI, but none of the anthropometric parameters showed significant relation. On the contrary, E-selectin levels correlated with anthropometric measures. ODI showed significant relation with E-selectin as well.

Associations between ODI and concentrations of vascular adhesion molecules adjusted for obesity and all the components of metabolic syndrome were tested using partial correlation analysis (Table 4). Adjustment for the components of metabolic syndrome eliminated significance between sVCAM levels and ODI, though it was still significant after adjustment for BMI and arterial hypertension.

Discussion

A limited number of studies have examined the levels of vascular cellular adhesion molecules such as sVCAM and E-selectin in OSA. This is one more study demonstrating that sVCAM and E-selectin concentrations were higher in OSA patients groups compared to the controls even though the control group was formed from snorers. Polysomnography helped to reject possible impact of intermittent hypoxia in activation of vascular adhesion molecules in the control group. As it is shown in Table 1, for neither AHI nor ODI—the hallmark of intermittent hypoxia exceeded normal ranges in the control group.

Association between OSA and the development of cardiovascular diseases is being widely investigated in the recent years. Several confounding variables in the development of these conditions have been well established. They are age, gender, smoking, and obesity [21]. Only men were included in

Table 1 Characteristics of the controls and the obstructive sleep apnea patients

Characteristic	Control group (n=13)	OSA group (n=65)	p value
Age (years)	33 (29–44)	40 (35–46)	>0.05
Epworth sleepiness scale	9 (6–13)	11 (7–15)	>0.05
Body mass index (kg/m^2)	24.74 (23.72–27.75)	30.25 (28.37–35.84)	**<0.001**
Waist circumference (cm)	91.5 (87.5–96.7)	103.5 (97.0–117.0)	**0.001**
Polysomnographic parameters:			
Apnea/hypopnea index (events/h)	2.4 (2.0–3.0)	28.25 (14.45–70.20)	**<0.001**
Arousal index (events/h)	14.2 (10.6–22.45)	30.7 (21.3–56.6)	**<0.001**
Oxygen desaturation index (events/h)	2.9 (1.0–4.2)	30.25 (12.20–72.60)	**<0.001**
Average SpO_2 (%)	96.0 (95.0–97.0)	94.0 (92.0–95.5)	**<0.001**
Lowest SpO_2 (%)	91.0 (89.0–92.0)	83.0 (72.5–87.5)	**<0.001**
SpO_2<90 % (%TST)	0 (0–0.1)	2.5 (0.3–24.3)	**<0.001**
Blood parameters:			
Total cholesterol (mmol/l)	4.99 (4.83–5.60)	5.63 (4.97–6.64)	>0.05
High-density lipids (mmol/l)	1.02 (0.83–1.24)	0.90 (0.79–1.05)	>0.05
Low-density lipids (mmol/l)	3.07 (2.71–3.61)	3.59 (3.10–4.10)	>0.05
Triglycerides (mmol/l)	0.93 (0.79–1.06)	1.60 (0.96–2.41)	**0.003**
Glucose (mmol/l)	4.99 (4.29–5.31)	5.59 (5.31–6.07)	**0.001**
sVCAM-1 (ng/ml)	565.5 (518.9–678.1)	698.2 (627.7–798.3)	**0.003**
E-selectin (ng/ml)	49.7 (39.8–59.5)	64.9 (50.1–83.1)	**0.017**

Data is presented as median (25th and 75th percentiles). *Mann–Whitney U* test. Statistically significant differences are in bold.

Table 2 Prevalence of metabolic syndrome in patients with OSA and the controls

Component of metabolic syndrome:	Control group (n=13)	OSA group (n=65)	p value
Waist circumference >102 cm	2 (16.7)	36 (59.0)	<**0.05**
Triglycerides ≥1.77 mmol/l	1 (7.7)	27 (41.5)	<**0.05**
High-density lipids <1.0 mmol/l	5 (38.5)	39 (60.0)	>0.05
Glucose ≥5.6 mmol/l	0 (0)	14 (23.7)	<**0.05**
Hypertension	0 (0)	15 (23.4)	<**0.05**
Metabolic score (1–5 range)	0.6±0.3	2.0±1.2	<**0.05**

Data is presented as numbers (%) and mean±SEM. Statistically significant differences are in bold.

Table 4 Partial correlation coefficients between apnea/hypopnea index and vascular adhesion molecules adjusted for possible confounding factors

Oxygen desaturation index adjusted for:	*Ln* sVCAM-1		*Ln* E-selectin	
	r	p	r	p
Body mass index	**0.331**	**0.009**	0.005	0.966
Body mass index and hypertension	**0.317**	**0.013**	0.024	0.856
Waist circumference, hypertension, triglycerides, high-density lipids, and glucose concentrations	0.283	0.09	0.091	0.552

Statistically significant differences are in bold

r Partial correlation coefficient, not normally distributed variables are logarithmically (*ln*) transformed, p Significance

this study trying to control for gender confounder. All the men in this study were middle-aged and there was no difference in age between the control and OSA subjects. Smoking status was an exclusion criterion. Accurate selection of the study population is the stronger part of this study.

There is an on-going discussion about the impact of obesity on inflammatory changes in OSA. Obesity is a pro-inflammatory condition itself and most of OSA patients are obese [22]. It has been demonstrated that changes in body weight reduce OSA severity as well as levels of cytokines [23, 24]. Both sVCAM and E-selectin levels have been previously reported to be increased in obese patients [9, 25]. The pro-inflammatory state associated with obesity is thought to play a major role in endothelial cell activation in severely obese individuals [25]. Interesting data was presented in a study performed by Troseid et al. [26]. They have evaluated changes in cellular adhesion molecules (CAMs) in 32 subjects with metabolic syndrome in a 12-week trial evaluating the effect of physical exercise and pravastatin. Changes from baseline were studied, and correlations between changes in CAMs, anthropometric measures, regional fat distribution, glycemic control, and the adipocytokine TNF-a and adiponectin were investigated. No significant changes in sVCAM levels were observed in any of the intervention groups. When examining the whole study population regardless of intervention, changes in serum E-selectin were significantly correlated to changes in body mass index (r=0.48, p=0.006). In our study, partial correlation analysis has demonstrated that there was no significant relation between vascular adhesion molecules and ODI after adjustment for all the components of metabolic syndrome. On the contrary sVCAM-1 levels were related to AHI and ODI after adjustment for BMI in our study (Table 4).

Table 3 Correlation coefficients between vascular adhesion molecules and anthropometric and polysomnographic parameters patients with OSA

Parameter	sVCAM-1		E-selectin	
	r	p	r	p
Anthropometric parameters:				
Body mass index (kg/m^2)	0.191	0.13	**0.335**	**0.006**
Waist circumference (cm)	0.179	0.172	**0.330**	**0.009**
Polysomnographic data:				
Apnea/hypopnea index (events/h)	**0.341**	**0.006**	0.207	0.09
Arousal index (events/h)	**0.278**	**0.026**	0.131	0.30
Oxygen desaturation index (events/h)	**0.303**	**0.016**	**0.309**	**0.013**
Average SpO_2 (%)	−0.225	0.074	−0.153	0.223
Lowest SpO_2 (%)	−0.214	0.094	−0.038	0.767
SpO_2 <90 % (%TST)	0.236	0.069	0.205	0.104

Statistically significant differences are in bold.

r *Spearman's rho* coefficient; p significance

Zamarrón et al. have examined the impact of continuous positive airway pressure (CPAP) treatment on circulating levels of vascular endothelial markers including ICAM-1 and E-selectin [27]. After 1 year of treatment, no differences were found in E-selectin levels, but ICAM-1 levels were significantly decreased. Another interventional study performed by Kazuo et al. had showed the effect of treatment of OSA by nasal continuous positive airway pressure (CPAP) on soluble cell adhesion molecules [28]. A positive impact of 1-month CPAP treatment on sICAM-1 and E-selectin but not sVCAM-1 was detected suggesting that elevation of those vascular adhesion molecules was triggered by OSA. It was also reported that the same changes were observed in the groups of OSA patients who did not lose weight and who did [28].

Having all this data, it is obvious that the relations between obesity, metabolic syndrome, and OSA are very complicated and complex. Studies including different treatment modalities could elucidate these interactions. The limitation of this study was that no treatment trial was planned in the protocol.

Conclusions

Higher levels of sVCAM-1 and E-selectin were detected in OSA patients compared to the controls. In the OSA patient group, levels of sVCAM-1 and E-selectin showed direct association with ODI, but this association was no more significant after adjustment for all the components of metabolic syndrome. After adjustment for possible confounding factors of impaired endothelial function in OSA—obesity and arterial hypertension, sVCAM-1 levels still were related to ODI.

Interactions between impairment of endothelial function and metabolic changes in OSA are closely related and the mechanisms remain unclear. Further studies including the impact of OSA treatment may serve for clarifying these interactions. In clinical practice, it could be useful to screen all the patients with OSA for metabolic syndrome as well as OSA should be suspected to the patients with metabolic syndrome.

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Conflict of interest The authors declare that they have no conflict of interest regarding this manuscript.

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