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CLINICAL STUDY

Relation between carotid intima-media thickness, serum paraoxonase levels and severity of obstructive sleep apnea syndrome

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ABSTRACT

INTRODUCTION: Obstructive sleep apnea (OSA) has a significant effect on the development of cardiovascular complications. The aim of this study was to evaluate the relationship between carotid intima-media thickness (IMT), paraoxonase 1 (PON 1) enzyme levels and severity of OSA.

MATERIAL AND METHODS: A total of 120 cases were included in the study with 30 cases in each group, as follows: Group 1 (AHI < 5/h), Group 2 (AHI 5–15/h), Group 3 (AHI 16-30/h) and Group 4 (AHI > 30/h). Blood samples of the patients were taken to measure serum PON1 activity. Carotid IMT of all patients included in the study was measured by means of echocardiography using vascular probe and results were recorded.

RESULTS: With regard to carotid IMT, a statistically significant increase was detected as severity of OSA increased ($p < 0.001$). A positive relationship was detected between IMT level and total oxygen desaturation time, oxygen desaturation index and SpO2 time < 90 % ($p < 0.01$). When the groups were compared, a statistically significant decline was observed in serum PON 1 level as severity of OSA increased ($p < 0.05$).

CONCLUSIONS: The findings of our study indicate that PON1 and carotid IMT might be used as indicators of vascular damage in patients with OSA. Depending on the severity of OSA, measurement of PON1 enzyme activity in conjunction with carotid IMT may help us in predicting the cardiovascular risk in patients with OSA *(Tab. 4, Fig. 2, Ref. 27)*. Text in PDF *www.elis.sk*

KEY WORDS: carotid intima-media thickness, obstructive sleep apnea, paraoxonase.

Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive apnea-hypopnea episodes in upper airways accompanying oxygen desaturations during sleep (1). Hypoxemia, oxidative stress and systemic inflammation, elevation in intrathoracic negative pressure and sympathetic overactivity due to intrapleural pressure fluctuations occur as the result of obstruction during sleep. These events play a common role in most of the OSA cases and in the development of many cardiovascular, endocrinologic, neurologic diseases (2).

Hypoxemia-reoxygenation cycles, formation of reactive oxygen and nitrogen species precipitate atherosclerosis. Increased oxidative stress, inflammation, coagulation disorders, metabolic disorders and vascular endothelial dysfunction accompany this process (3). Paraoxonase 1 (PON 1) enzyme is a high-density lipoprotein (HDL)-related enzyme which shows esterase and lactonase activity (4). This enzyme acts as an important antioxidant against oxidative stress and is associated with pathogenesis of many diseases, mainly cancer and cardiovascular diseases. Studies have indicated that calcium-bound paraoxonase on HDL has an important physiologic role in metabolism of oxygenated lipids and for preventing atherosclerosis. The relationship between PON1 and atherosclerosis is attributed to anti-atherogenic properties of HDL (5).

The changes beginning with increased carotid artery intima-media thickness (IMT) due to oxidative stress and systemic inflammation in OSA lead to atherosclerosis, luminal narrowing and occlusion (6). The increase in carotid artery IMT is an independent risk factor for cerebrovascular diseases (7).

Evaluation of carotid artery intima-media thickness (an early sign of atherosclerosis), change in paraoxonase serum level (an indicator of oxidative damage) and the investigation of the relationship between these two parameters and the severity of OSA are the main objectives of our study.

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Materials and methods

This study was approved by the Research Committee of the Medical Faculty and Health Sciences, Baskent University (project# KA 13/117) and supported by the Research Fund of Baskent University. Written informed consent was obtained from each participating patient prior to the study.

One hundred and twenty volunteers who were admitted to Sleep Disorders Center with symptoms of nocturnal snoring and/or excess daytime sleepiness were included in the study. Standard overnight polysomnography (PSG) was performed with one night hospitalization in the sleep laboratory between May 2013 and January 2014.

Patient groups

A total of 120 volunteers whose polysomnographic examination was scored manually, aged between 18–65 years, who met the inclusion and exclusion criteria, were included in our study. The patients whose AHI was < 5/h were accepted as primary snoring/control group (group 1). The patients whose AHI was > 5/h were accepted as OSA and grouped according to the stage. Thirty volunteers were enrolled in each group: the subjects whose AHI = 5–15/h (mild OSA) were evaluated as group 2, AHI = 16–30/h (moderate OSA) group 3, AHI > 30/h (severe OSA) as group 4.

Exclusion criteria

Patients who had a disease known to affect PON1 and IMT level were excluded from the study. These included: coronary artery disease (CAD), cerebrovascular disease, uncontrolled hypertension, diabetes mellitus (DM), antihyperlipidemic drug use, malignity, active smoking, chronic obstructive pulmonary disease, asthma, allergic rhinitis, connective tissue disease, history of an infectious disease within the past month, and diagnosis of a neuromuscular disease.

Polysomnography

Standard overnight polysomnography (Astro-Med Grass-telefactor, RI, USA) was performed in all patients. This included electroencephalography (C4-M1, C3-M2, O2-M1, and O1-M2), electrooculography, and electromyography (from mandibular and tibialis anterior muscle). Oronasal air flow was measured with thermistor and nasal cannula, thoracoabdominal movements, and body position. Blood oxygen saturation was measured with pulse oximeter. Electroencephalography electrodes were positioned according to the international 10–20 system. Sleep was recorded and scored according to the standard method8. Apnea was defined as a drop ≥ 90 % of baseline in airflow that lasts for longer than 10 seconds. Hypopnea was defined as a ≥ 30 % reduction in oronasal flow amplitude ≥ 10 seconds, accompanied by ≥ 3 % desaturation or arousal. Classification of hypopnea and apnea as obstructive, central, or mixed was performed by calibrated respiratory inductance plethysmography. The oxygen desaturation index (ODI) is the number of times per hour of sleep in which the blood's oxygen level drops by ≥ 3 percent from baseline.

Laboratory analysis

Blood samples of the patients were taken for the measurement of serum paraoxonase (PON1) activity. Serum samples used in the study were centrifuged at 1000xg for 15 min and kept at –20 °C until analysis. Serum PON activity was studied according to the method described by Jerzy Beltowoski (148). Phenylacetate was used as substrate and PON activity was determined by measuring hydrolysis rate of phenylacetate. Serum PON activity was examined by spectrophotometer (UV-1601 Shimadzu) record of absorbance at 270 nm for 1 min after adding 10 µl of serum sample onto 3 ml of the reactive (50 mM pH 8.0 Tris-HCL buffer, containing 2 mM CaCl2, 2 mM phenylacetate). Serum PON activity was calculated assuming E270 = 1310 $M^{-}1\ cm^{-}1$ (9).

Ultrasonography examination

Carotid artery intima-media thickness measurement was undertaken using a commercially available echocardiography device (Vivid I, GE Healthcare) using an 8 MHz linear vascular probe. In order to avoid interobserver variability, all measurements were carried out by the same physician using the same device. Procedure in each subject was initiated following a 15 min resting period in the supine position. The head was turned 10° to the opposite side for carotid artery measurement. After the ultrasound transducer was placed on the long axis of the carotid artery at a 90° angle, it was

Tab. 1. Demographic characteristics of the study groups.

Demographic characteristics	Group 1 (n: 30)	Group 2 (n: 30)	Group 3 (n: 30)	Group 4 (n: 30)	p
Gender					
Female	10	8	3	6	0.176
Male	20	22	27	24	
Age (years)					
Mean±SD	43.7±9.6	43.6±9.3	46.8±10.3	46.7±11.0	0.358
(min – max)	(27–61)	(26–60)	(29–62)	(28–68)	
Body weight (cm)					
Mean±SD	170.6±9.3	171.6±8.2	172.5±8.7	173.9±8.1	0.510
(min – max)	(150–190)	(155–186)	(150–188)	(158–190)	
Height (kg)					
Mean±SD	75.4±14.3	85.0±14.2	91.2±13.4[a]	94.1±17.3[b]	<0.001
(min – max)	(49–103)	(58–120)	(68–123)	(66–140)	
BMI (kg/m^2)					
Mean±SD	25.9±4.5	28.7±3.6	30.7±5.0[a]	31.0±4.9[b]	<0.001
(min – max)	(17.7–36.4)	(23.2–37.1)	(24.6–49.7)	(24.8–45.7)	
Neck circumference (cm)					
Mean±SD	37.6±3.7	40.5±3.4[c]	41.0±3.0[a]	41.4±2.9[b]	<0.001
(min – max)	(30–44)	(34–50)	(32–48)	(36–51)	

Data are expressed as mean ± SD for parameters with normal distribution and median for parameters with skewed distribution (range min–max), BMI – body mass index. Where p is significant, values within a row with the same superscript letter are significantly different. [a] $p < 0.05$ between group 3 and group 1, [b] $p < 0.05$ between group 4 and group 1, [c] $p < 0.05$ between group 2 and group 1

Tab. 2. Polysomnographic characteristics of subjects (n = 120).

VARIABLES (Mean±SD)	Group 1	Group 2	Group 3	Group 4	p
Total sleep time (min)	329.0±37.1	341.2±46.3	337.2±40.8	330.4±49.4	0.683
Stage N1 (min)	12.0±7.3	11.5±5.5	14.6±10.3	12.8±7.8	0.484
Stage N2 (min)	172.4±38.8	183.3±35.1	177.9±37.5	209.4±55.6[a,b]	<0.05
Stage N3 (min)	86.8±33.2	80.1±28.5	84.0±31.7	52.9±42.2[a,b,c]	<0.001
Stage REM (min)	57.6±21.5	66.1±24.0	60.5±20.0	55.3±25.7	0.283
AHI (/h)	2.5±1.3 (0.2–4.9)	9.1±2.7[d] (5.5–14.6)	23.4±4.7[e,f] (15.9–29.8)	63.2±26.5[a,b,c] (31.8–120.9)	<0.001
Apnea index (/h)	0.2±0.5 (0–2)	1.6±1.7[d] (1–7.1)	7.1±5.6[e,f] (0.4–24.1)	44.3±79.2[a,b,c] (1.80–441)	<0.001
Hypopnea index (/h)	2.2±1.2 (0–4.9)	7.4±2.4[d] (2.3–11.3)	16.3±5.9[e,f] (4.7–27.7)	34.1±21.5[a,c] (0.2–112.5)	<0.001
Arousal Index (/h)	7.7±3.7	13.2±11.5	15.5±9.7[e]	51.3±69.8[a,b,c]	<0.001
Total O2 desaturation	10.3±7.3	41.6±24.8[d]	100.8±40.1[e,f]	285.7±163.8[a,b,c]	<0.001
ODI (n/h)	1.5±1.0	6.2±3.7[d]	15.1±5.6[e,f]	44.3±26.3[a,b,c]	<0.001
Min. SpO_2	82.0±12.8	83.1±7.6	75.5±9.6[e,f]	70.4±12.2[a,c]	<0.001
Time that SpO2<90% (%)	2,2±5,8	4,5±6,9	15,9±20,8[e,f]	32,6±27,4[a,c]	<0,001

AHI – apnea hypopnea index; ODI, oxygen desaturation index. Where P is significant, values within a row with the same superscript letter are significantly different. [a] $p < 0.05$ between group 4 and group 1, [b] $p < 0.05$ between group 4 and group 3, [c] $p < 0.05$ between group 4 and group 2, [d] $p < 0.05$ between group 2 and group 1, [e] $p < 0.05$ between group 3 and group 1, [f] $p < 0.05$ between group 3 and group 2

Tab. 3. The association between PON 1 activity and groups.

	PON1 activity (U/ml) Mean±SD (min – max)
Group 1	125.7±18.0 (99.6–164.7)
Group 2	117.2±19.9 (78.6–155.0)
Group 3	110.4±23.7[a] (64.8–141.3)
Group 4	109.7±19.8[b] (60.5–143.8)

PON 1; paraoxonase 1 enzyme levels. Where p is significant, values within a row with the same superscript letter are significantly different. [a] $p<0.05$ between group 3 and group 1, [b] $p < 0.05$ between group 4 and group 1

Tab. 4. Carotid intima-media thickness values according to groups.

	IMK (mm) Mean±SD (min – max)	p
Group 1	0.4±0.08 (0.4–0.7)	<0.001
Group 2	0.5±0.09 (0.4–0.8)	
Group 3	0.7±0.14 (0.6–1.2)	
Group 4	0.8±0.12 (0.7–1.2)	

directed toward parallel echo lines of intima and media walls. The distance in intima-lumen interface and media-adventitia interface was measured. Measurements were obtained from both the right and the left carotid artery.

Statistical analysis

Data was evaluated in SPSS, Chicago IL, Version 17 package program. First, descriptive statistics of continuous variables were given. Descriptive statistics were expressed as mean ± standard deviation and frequency (%). Variables were evaluated after control of normality and homogeneity of variances had been undertaken (Shapiro-Wilk and Levene test). When carrying out data analysis, an independent paired t test (Student's t test) was used for comparison of two groups, Mann-Whitney U test was used when preconditions were not available. One way variance analysis was carried out for comparison of three or more groups, and Kruskal-Wallis test was used when preconditions were not available with Tukey HSD and Bonferroni-Dunn tests. The association between continuous variables was evaluated with Pearson correlation coefficient and Spearman correlation coefficient was used when parametric test preconditions were not provided. Chi-square and Fisher exact test were used for analysis of categorical data. p values of ≤ 0.05 were accepted as statistically significant.

Results

A total of 120 cases were included in the study with 30 cases in each group as follows: Group 1 (AHI < 5/h), Group 2 (AHI 5–15/h), Group 3 (AHI 16–30/h) and Group 4 (AHI > 30/h). Of the patients, 77.5 % were male and 22.5 % were female. The mean age was 45.3 ± 10.1 years (range 26–68). Body weight, BMI, and neck circumference were significantly greater in cases within Groups 3 and 4 ($p < 0.001$). Demographic characteristics of the cases regarding groups are given in Table 1.

When PSG parameters of the cases were analyzed, a significant difference was not observed between groups regarding total sleep time, sleep efficiency, total stage N1 time and REM time. While apnea index, hypopnea index, arousal index, ODI, SpO2 < 90 % time were increased, minimum SpO2 and total stage N3 time were lower in severe OSAS, as expected. The changes in these parameters were correlated with AHI which defines the severity of OSA. PSG parameters of the cases are shown in Table 2.

When the groups were compared, a statistically significant decline was observed in serum PON1 levels as severity of OSA increased ($p < 0.05$). The association between paraoxonase levels and PON 1 among groups are shown in Table 3 and Figure 1. A 20.2 % negative linear correlation was detected between PON1 level and total oxygen desaturation time. A 19.9 % negative correlation between PON1 level and ODI was detected as well as a 23.5 % negative linear correlation between PON1 level and SpO2 time < 90 % ($p < 0.05$).

With regard to carotid IMT, a statistically significant increase was detected as severity of OSA increased ($p < 0.001$). Carotid intima-media thickness values according to groups are shown in

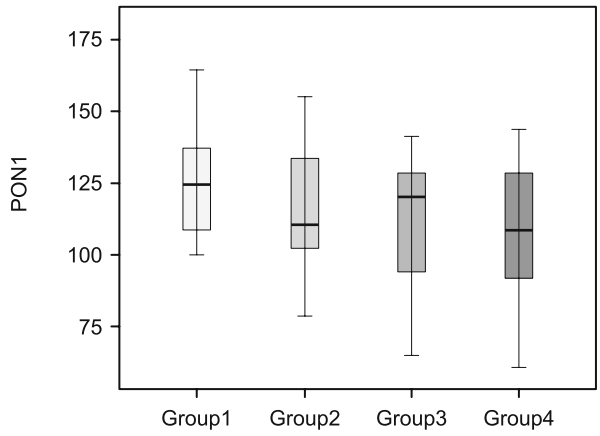

Fig. 1. The association between PON 1 activity and groups.

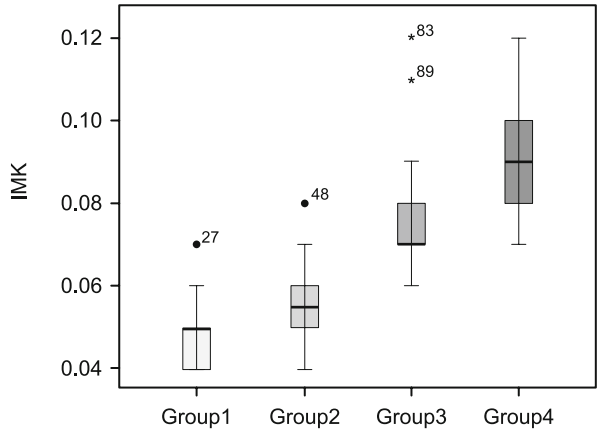

Fig. 2. The relationship between carotid intima-media thickness values and each group.

Table 4 and the relationship between IMT and each group is seen in Figure 2. A positive 55.9 % relationship was detected between IMT level and total oxygen desaturation time; positive 55.5 % relationship between IMT level and ODI; and positive 45.5 % linear relationship between IMT level and SpO2 time < 90 % ($p < 0.01$).

As OSA severity increased, there was a rise in IMT and a decrease in PON 1 levels. There was a significant 29.9 % negative correlation between IMT and PON 1 concentration ($p < 0.005$).

Discussion

Obstructive sleep apnea syndrome leads to sleepiness as a result of sleep interruption, hypoxemia because of upper airway obstruction and sympathetic activation as a result of arousals. Recurrent hypoxia/reoxygenation cycle and oxidative stress play a role in the beginning of cardiovascular complications in untreated OSA patients (10).

Studies have shown that oxidative stress plays an important role in pathogenesis of atherosclerosis. LDL in serum converts to oxidant LDL form, which is atherogenic, foam cells are formed as the result of accumulation of oxidant products and consequently atheromatous plaque develops. In studies conducted by considering that serum PON activity plays a protective role in the early stage of this process, paraoxonase was shown to have a protective effect against atherosclerosis through hydrolysis of phospholipids (11). H2O2 is a reactive oxygen metabolite which leads to LDL oxidation through being converted to potent radicals during oxidative stress. PON1's hydrolysing property of H2O2 plays an important role in elimination of oxidants formed during atherosclerosis (12).

Paraoxonase gene family is composed of three enzymes as interrelated PON1, PON2 and PON3 which are located on the long arm of 7q 21.3–22.1 chromosome in humans. PON1, which is synthesized in the liver and released into the circulation, is a protein weighing 43 kDa of molecular weight, composed of 354 amino acids, and usually localized on HDL in serum (13, 14). PON1 takes part in the structure of HDL cholesterol and presents lipoprotein oxidation by hydrolysis lipid peroxides in the structure of LDL. It was considered to be protective against atherosclerosis due to this property and this effect was shown in invitro studies12. Studies have shown that serum PON1 activity decreased in CAD, HL and DM and decreased lipid peroxidation in carotid atherosclerotic lesions (15, 16).

Lipid peroxidation and oxidative stress are known to play a key role in the development of atherosclerosis (17). OSA patients are exposed to oxidative stress during the night. Therefore, lipid peroxidation and oxidative stress seen in OSA patients were considered to play an important role in pathogenesis of cardiovascular disease. In the study of Barcelo et al comparing 40 severe OSA patients with control group, OSA was associated with abnormal lipid peroxidation and this condition was emphasized to be a factor to explain the widespread prevalence of cardiovascular disease in OSA (18). Lavie et al allocated the cases to three groups as control group, OSA group and OSA +CAD group and detected that PON1 level was higher in control group compared to other groups ($p < 0.05$) (19). In another study, Vatansever et al concluded that PON1 activity did not differ between OSA group and control group, PON1 activity changed only in the group where OSA and cardiovascular disease coexisted (20).

PON1 activity was measured in primary snoring (control group), mild, moderate and severe OSA groups in our study. When the groups were compared, a statistically significant decrease was detected in PON1 serum levels as OSA severity increased. Detection of a negative linear relationship between PON1 level and total oxygen desaturation time, ODI, time where SpO2< 90 %, suggested that nocturnal hypoxemia in OSA patients was associated with the reduction in PON1 value, which is an indicator of decrease in antioxidant capacity and increase in oxidative stress. Hypoxia/reoxygenation cycle repeats during sleep in OSA patients and developing oxidative stress may play a role in development of cardiovascular complications. Reduced antioxidant capacity in serum is an indicator of excessive oxidative stress. The imbalance between oxidative stress and antioxidant level plays an important role in pathophysiologic relationship between hypoxia and cardiovascular disease in OSA patients. PON1 enzyme activity measurement gives an idea of antioxidant capacity. In our study, decreased

PON1 activity as disease severity increased suggests that PON1 activity level may be an indicator for prediction of cardiovascular complication risk in OSA patients.

Apnea-related hypoxia leads to free oxygen radical formation in OSA, and this process progresses to atherosclerosis. Increase in IMT is usually inevitable in OSA cases and leads to atherosclerosis over time. Carotid arteries which provide cerebral blood supply are also affected from these alterations. The changes beginning with IMT increase lead to atherosclerosis and narrowing in the lumen (21). The influence of OSA on atherosclerosis development was shown in the studies measuring carotid IMT. In one study conducted in patients with no known cardiovascular disease, Baguet et al showed that low oxygen saturation values during sleep lead to carotid plaque development (22). Silvestrini et al detected that carotid IMT values were statistically significantly higher in severe OSA patients compared to control group (6). Mean IMT was found significantly higher in severe OSA group compared to control group and mild-moderate OSA group in the study by Fox et al (23). Apaydın et al found IMT values higher in OSA group compared to habitual simple snoring group however a correlation was not detected between OSA severity and IMT (24).

In our study, when groups were compared, a statistically significant increase was detected in IMT values as OSA severity increased, a positive linear correlation was detected between IMT values and total oxygen desaturation time, ODI and time where SpO2 < 90 %.

Carotid IMT measurement is a non-invasive method which enables early detection of atherosclerotic changes in vascular bed, producing risk classification for cardiovascular mortality and morbidity. Our findings suggest that carotid IMT level may be a non-invasive marker for detection of cardiovascular complications of OSA.

Studies using different inflammatory markers like interleukin (IL)-18, CRP, IL-6, Tumor necrosis factor (TNFα) and Pentraxin-3, demonstrated that there is a relationship between such markers and IMT in OSA (25, 26). The mean carotid IMT values were reported to be higher in moderate and severe OSA groups compared to control group. They showed a positive linear relationship between IMT and inflammatory markers. The authors concluded that recurrent hypoxia-reoxygenation episodes and sleep fragmentation led to systemic inflammation characterized by increased inflammatory markers and this inflammation plays an important role in atherosclerosis development. Monneret et al investigated urinary 15-F2t-isoprostane levels, an oxidative stress marker, and carotid IMT measurements in non-obese OSA patients. Urinary 15-F2t-isoprostane levels and carotid IMT measurements were found significantly higher in severe OSA group compared to controls (27).

In our study, an increase was detected in carotid IMT, an early indicator of atherosclerosis and a decrease was detected in serum PON1 levels, a marker of oxidative stress as OSA severity increased. When the relationship between these two parameters was analyzed, a negative correlation was detected between PON1 level and IMT. Detection of a correlation between PON1 and carotid IMT suggests that PON enzyme activity may be used as an indicator of vascular injury in OSA patients. Our findings indicate that PON1 enzyme activity and carotid IMT measurement might be used to estimate vascular disease in patients with OSA.

Conclusion

The findings of our study indicate that there is a correlation between PON1 and carotid IMT demonstrating that paraoxonase enzyme activity could be used as an indicator of vascular damage in patients with OSA. Depending on the severity of OSA, measurement of PON1 enzyme activity in conjunction with carotid IMT may help us in predicting cardiovascular risk in patients with OSA.

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