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RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

Carotid Intima-Media Thickness in Patients with Obstructive Sleep Apnoea Syndrome

Obstrüktif Uyku Apne Sendromlu Hastalarda Karotis İntima Media Kalınlığı

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ABSTRACT

Objective: This study was performed retrospectively to evaluate the relationship between smoking, weight, biochemical, and hematological parameters and Common Carotid Artery- Intima Media Thickness (CCA-IMT) in patients with obstructive sleep apnoea syndrome (OSAS).

Methods: 96 OSAS patients aged between 30 and 76 years (Average = 47 ±12), and 48 control subjects aged between 22 and 75 years (Average = 53 ±11) were evaluated. Doppler ultrasonography was used to measure CCA-IMT of subjects, grouped based on Apnoea hypopnea index (AHI), smoking habit, and body mass index (BMI).

Results: It is observed that CCA- IMT increases in OSAS patients. The hemoglobin and hematocrit values were significantly different in the OSAS group against the controls. This can be attributed to an increase in erythrocyte due to hypoxia. The levels of triglyceride, CRP, and homocysteine were found to be higher in patients than in controls, though not statistically significant.

Conclusions: Sleep apnoea-related hypoxia has hazardous effects on human health. Hypoxia and apnoea that constitutes an important percentage of disordered breathing events seem to contribute heavily to an increase in IMT. Additionally, CCA-IMT is highly related to smoking; yet even in non-smokers, OSAS is an independent risk factor.

Keywords: Obstructive sleep apnoea syndrome, Smoking, CCA-IMT, Doppler USG

ÖZET

Amaç: Bu çalışmada Obstrüktif Uyku Apne Sendromu (OUAS) hastalarında Common Karotis Arter - Intima Media Kalınlığı (CKA-IMK) ile sigara kullanımı, kilo, biyokimyasal ve hematolojik parametreler arasındaki ilişki retrospektif olarak değerlendirildi.

Yöntem: Doppler Ultrasonografi ile 96 OUAS hastası yaşları 30-76 yaş aralığında (ortalama = 47 ± 12) ve 48 kontrol vakası 22-75 yaş aralığında (ortalama = 53 ± 11) değerlendirildi. Apne Hipopne İndeksi (AHİ), sigara içme alışkanlığı ve Vücut Kitle İndeksine (VKİ) grup temelinde CKA-IMK ölçümleri değerlendirildi.

Bulgular: OSAS hastalarında CKA-IMK'nın arttığı gözlendi. OSAS grubunda hemoglobin ve hematokrit değerleri kontrollere göre anlamlı olarak farklıydı. Bu, hipoksi nedeniyle eritrosit artışına bağlanabilir. Trigliserit, CRP ve homosistein düzeyleri, istatistiksel olarak anlamlı olmasa da, kontrol grubundakinden daha yüksek bulundu.

Sonuç: Uyku apnesine bağlı hipoksinin insan sağlığı üzerinde tehlikeli etkileri vardır. Bozulmuş solunum olaylarının önemli bir yüzdesini oluşturan hipoksi ve apne, intima media kalınlığındaki (IMK) artışa büyük ölçüde katkıda bulunur. Ek olarak, CKA-IMK sigarayla oldukça ilgilidir. Yine de sigara içmeyenlerde bile, OSAS bağımsız bir risk faktörüdür.

Anahtar Sözcükler: Obstrüktif uyku apne sendromu, sigara, CKA-IMK, Doppler USG

INTRODUCTION

Obstructive sleep apnoea syndrome(OSAS) is a disease characterized by episodes of upper airway obstruction and reductions in oxygen saturation, during sleep. OSAS is a common and serious health problem.[1, 2]

In adult populations, OSAS prevalence is 1.2-2.5% in women and 1-5% in men.[3] Epidemiological studies have reported that OSAS prevalence in Turkey is 1.8%.[4] The

relationship between OSAS and cardiovascular disease has been studied for years, and OSAS has been identified as an independent risk factor for cardiovascular diseases.[5, 6] More than half of the patients with cerebrovascular diseases suffer from OSAS.[7,8] OSAS is characterized by inflammation caused by free oxygen radicals and nitric oxide, endothelial damage, and smooth muscle proliferation in the wall of vessels.[9-11]

METHODS

Patients referred to Hendek Government Hospital Sleep Laboratory, between January 2012 and January 2013, were included in this study. The test results were evaluated by the same doctor. Before polysomnography, the participants were asked to fill a questionnaire to assess the sleep-related symptoms. Based on this questionnaire, basic OSAS symptoms like snoring, apnoea, and daytime somnolence were assessed. Epworth sleepiness scale was used to evaluate daytime somnolence. ENT evaluation was performed. After each patient in the study was examined, the patients were invited for all-night polysomnography at our sleep disorders laboratory. Patients were informed in advance not to take any drink or food containing caffeine, sleep medications (antihistamines, antidepressants, hypnotics, etc) or alcohol, and not to sleep during the day of polysomnography.

Polysomnography

Polysomnography (PSG) (Compumedics, Melbourne, Australia, Model: Somte PSG, Ser. No: 3127 CAB2-06), Electroencephalography (EEG), electrooculography (EOG), chin electromyography (EMG), oral and nasal airflow (nasal-oral thermistor and nasal cannula), thorax movements, abdominal movements, arterial oxygen saturation, ECG, and snoring records (>6 hours) were obtained.

OSAS patients and controls were grouped according to their age (<40, 40-50, and >50). Patients with AHI <5 were considered as the control group, while OSAS patients were divided into 3 subgroups (AHI < 15, 15 ≤ AHI < 30, and 30 ≤ AHI). Patients were classified according to their smoking status (non-smoker, smoker, and ex-smoker). Cigarette smoke exposure was calculated as packs/year and grouped into 3 subgroups (<10, 10-20, and >20 packs/year). A signed informed consent form was obtained from each patient.

The exclusion criteria included hypertension, cerebrovascular and peripheral vascular diseases, systemic diseases requiring prescription medications, and drug abuse. Systolic and

diastolic blood pressure and heart rate were within the normal range in both the patients and the controls. None of the subjects had diabetes, hypercholesterolemia, or BMI >30.

Doppler ultrasonography

CCA-IMT measurements were made from anterior and posterior walls using a standard 5-10 MHz linear transducer using the same bidirectional Doppler system (DC-T6 Ultrasound System, Shenzhen Mindray Bio-Medical Electronics Co. Ltd., China) by the same, experienced radiologist.

Patients were evaluated in a dark room, in the supine position, by holding the Doppler probe slightly inclined parallel to carotid lumen diameter, and images were manipulated to obtain the best image. The average of measurements from three neighboring regions was recorded as carotid artery intima-media complex.

The measurements were made from both right and left carotid arteries, in proximal CCA without plaques, 1.5 cm away from the carotid bulb.

Biochemical analyses

The blood samples were centrifuged within 30 minutes after collection, and the samples were stored at -40 °C until analysis. All samples were analyzed in a single session.

Serum fasting total homocysteine, cholesterol, triglyceride, and glucose levels were measured using calibrators and kits in a biochemical analyzer (Olympus AU 640 Analyzer, Olympus Corporation, Tokyo, Japan).

Statistical analysis

Paired t-test and Kruskal-Wallis test were used to compare carotid intima-media thickness and other continuous parameters between the two groups. Dunn's test was used to compare pairs of the group. Continuous variables were presented as an average ±standard deviation. Chi-square test was used to examine the association between categorical variables and presented as number and percentage. Pearson's correlation coefficients were used to determine the correlation between carotid intima-media thickness and other parameters. P-value <0.05 was considered significant. All the analyses were made using commercial software (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY).

Regression analyses were performed on factors that affect IMT in OSAS patients. Smoking status and duration, total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein, and BMI were evaluated. IMT measurement was made in 3 neighboring regions

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and averaged. The groups were compared with Student's t-test or Mann-Whitney U test. P-value of <0.05 was considered statistically significant. One-way ANOVA was used to compare subgroups according to the duration of exposure.

RESULTS

The ages of all the subjects were between 22 and 76 years (Average = 53 ±11). The control group consisted of 46 patients aged between 22 and 45 years (Average = 47 ±13). The OSAS group consisted of 96 volunteers aged between 30 and 76 years (Average = 53 ±11) (Table 1). The two groups were not identical in terms of age and gender distribution, as the OSAS group consisted more of male and older patients. No significant difference in height was found between the groups; however, the difference between their weights was statistically significant. BMI was higher in the OSAS group, even though not statistically significant. This could be due to the OSAS patients being slightly taller. When CCA-IMT patients were compared with the control groups, the difference was found to be significant in mild OSAS patients with AHI 5-15, those younger than 50 years of age, those who smoked <20 packs/year, non-smokers, and smokers (Table 2).

It is plausible that smoking contributes to the difference between the two groups, but the difference between non-smoking patients against controls demonstrates that OSAS alone can cause an increase in CCA-IMT probably due to hypertension and hypoxia.[12,13]

The absence of this difference between ex-smokers might explain the fact that smoking has a comparable effect between the two groups, and that OSAS might not contribute significantly to an additional effect.

DISCUSSION

Obstructive sleep apnoea (OSA) is correlated with increased cardiovascular morbidity and mortality. As in the case of smokers and OSAS patients, exposure to carbon monoxide, nitric oxide, and free radicals might contribute to an increase in IMT.[14-16]

When OSAS and control groups were compared in terms of CCA-IMT, the difference was found to be significant in mild OSAS patients with an AHI between 5 and 15, those younger than 50 years of age, ex-smokers, who smoked < 20 packs/year, non-smokers, and current smokers. It is plausible that smoking contributes to the difference between the two groups, but the difference between non-smoking patients against controls demonstrates that OSAS alone

can cause an increase in CCA-IMT, probably due to sequelae like hypertension and hypoxia. The absence of difference between ex-smokers might indicate that smoking has the same effect between two groups, and OSAS might not have an additional effect.

The cholesterol level in the OSAS group was found to be lower; this might be because obese patients tend to care more about their diet. Statistically lower levels of HDL can be attributed to lack of exercise.[17] Triglyceride, CRP, and homocysteine levels were found to be higher in patients than do controls, yet not in statistically significant proportions. An increased level of homocysteine has been proposed as an independent risk factor for atherosclerosis and cardiovascular diseases but its relationship with OSA remains a controversy. Hemoglobin and hematocrit values were significantly different in the OSAS group compared to the controls. This might be attributed to an increase in erythrocyte due to hypoxia.[18]

CONCLUSION

It is observed that carotid IMT increases in OSAS patients. Sleep apnoea-related hypoxia has hazardous effects on human health. Hypoxia apnoea that constitutes an important percentage of disordered breathing events seems to contribute heavily to an increase in IMT. Additionally, CCA-IMT is highly related to smoking; yet even in non-smokers, OSAS is an independent risk factor.

Table1. Comparison of patient characteristics between the patient and control groups.

		Control (n=46)	Patient (n=96)	p value
AHI	**0-5 (Control)**	46 (100)	0 (0)	**<0.001**
	5-15 (Slight)	0 (0)	16 (16.7)	
	15-30 (Mild)	0 (0)	7 (7.3)	
	>30 (Severe)	0 (0)	73 (76)	
Age	**<40**	9 (19.6)	11 (11.5)	0.193
	40-50	19 (41.3)	33 (34.4)	
	>50	18 (39.1)	52 (54.2)	
Gender	**Male**	26 (56.5)	75 (78.1)	**0.014**
	Female	20 (43.5)	21 (21.9)	
Smoking	**Non-Smokers**	23 (50)	43 (44.8)	0.565
	Smokers	18 (39.1)	36 (37.5)	
	Ex-Smokers	5 (10.9)	17 (17.7)	
Smoking (pack-years)	**None**	23 (50)	43 (44.8)	0.584
	<10	1 (2.2)	3 (3.1)	
	10-20	9 (19.6)	13 (13.5)	
	>20	13 (28.3)	37 (38.5)	
AHI		2.27±1.12	52.01±28.79	**<0.001**
Age		47.17±12.6	52.95±11.35	**0.007**
Height		167±8.54	169.48±8.15	0.097
Weight		78.74±13.57	85.08±11.31	**0.004**
BMI		28.21±4.29	29.55±2.74	0.056
IMT left		0.81±0.17	0.95±0.66	**0.008**
IMT right		0.82±0.16	0.91±0.25	0.151
Homocysteine		14.77±4.47	15.28±5.69	0.591
Hematocrit		40.39±6.96	42.78±5.14	**0.043**
Hemoglobin		12.41±3.4	13.99±2.28	**0.016**
LDL Cholesterol		130.76±39.61	121.3±34.77	0.149
HDL Cholesterol		45.68±11.31	41.24±9	**0.022**
Total Cholesterol		212.38±43.76	203.82±39.73	0.247
Triglycerides		192.41±91,15	217.17±102.22	0.164
C-Reactive Protein		4.46±7,76	7.45±9.55	0.102
Mean O_2 Saturation		94,87±1,41	88,78±4,62	**<0.001**
O_2 Desaturation İndex		2,08±1,05	50,45±27,37	**<0.001**
Minimum O_2 Saturation		88,43±2,21	73,27±10,13	**<0.001**

Table 2. Comparison of carotid intima media thickness among several characteristics for the control and patient groups.

		Control (n=46)			**Patient (n=96)**		
		n	**Left IMT (Mean±SD)**	**Right IMT (Mean±SD)**	**N**	**Left IMT (Mean±SD)**	**Right IMT (Mean±SD)**
AHI	**0-5 (Control)**	46	0.81±0.17	0.82±0.16	0	-	-
	5-15 (Slight)	0	-	-	16	0.76±0.11	0.79±0.12
	15-30 (Mild)	0	-	-	7	0.91±0.23	0.91±0.23
	>30 (Severe)	0	-	-	73	0.99±0.75 [a]	0.93±0.27
	p-value		-	-		**0.032**	0.141
Age	**<40**	9	0.67±0.07	0.72±0.1	11	0.76±0.09	0.75±0.14
	40-50	19	0.79±0.15	0.83±0.16	33	1±1.1	0.87±0.28
	>50	18	0.89±0.18 [a]	0.86±0.16	52	0.96±0.22 [b.c]	0.97±0.23 [b.c]
	p-value		**0.002**	0.102		**0.002**	**0.001**
Gender	**Male**	26	0.83±0.18	0.85±0.17	75	0.99±0.74	0.93±0.26
	Female	20	0.78±0.16	0.78±0.13	21	0.81±0.18	0.84±0.19
	p-value		0.273	0.154		0.290	0.139
Smoking	**Non-Smokers**	23	0.74±0.13	0.76±0.12	43	0.84±0.19	0.87±0.21
	Smokers	18	0.83±0.15	0.85±0.15	36	1.09±1.04	0.94±0.29
	Ex-Smokers	5	1.02±0.22 [d]	0.98±0.18 [d]	17	0.94±0.25	0.94±0.25
	p-value		**0.009**	**0.008**		0.168	0.506
Smoking (pack-years)	**None**	23	0.74±0.13	0.76±0.12	43	0.84±0.19	0.87±0.21
	≤20	10	0.77±0.18	0.79±0.15	16	0.82±0.13	0.83±0.19
	>20	13	0.95±0.15 [e.f]	0.95±0.14 [e]	37	1.14±1.02 [f]	0.99±0.29 [f]
	p-value		**0.001**	**0.001**		**0.019**	**0.045**

According to pai wise comparison of Kruskall Wallis test; [a]: Statistically significantly different from AHI=5-15 group, [b]: Statistically significantly different from Age<40 group, [c]: Statistically significantly different from Age=40-50 group, [d]: Statistically significantly different from non-smoker group, [e]: Statistically significant different from none pack-years group, [f]: Statistically significantly different from ≤20 pack-years group, other pairwise comparisons were not statistically significant.

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