DETERMINATION OF SUBCLINICAL ATHEROSCLEROSIS IN OBSTRUCTIVE SLEEP APNEA SYNDROME PATIENTS WITHOUT TRADITIONAL RISK FACTORS FOR ATHEROSCLEROSIS

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ABSTRACT

Objective: *Obstructive sleep apnea-hypopnea syndrome (OSAS) is associated with high cardiovascular morbidity and mortality. Recent studies have suggested a pathophysiological link between OSAS and atherosclerosis; for which carotid intima-media thickness (CIMT) and pulse wave velocity (PWV) has been considered as an early marker. The aim of this study was to assess the presence of early signs of atherosclerosis and cardiovascular effects of OSAS depending on its severity, in patients without clinically diagnosed cardiovascular disease and any coincident risk factors for atherosclerosis.*

Material and Method: *Thirty one healthy subjects without any systemic disease and OSAS, and patients with OSAS without known atherosclerosis and also without any risk factors for atherosclerosis were examined in the study. According to the severity, 30 patients were in mild OSAS, 32 were in moderate OSAS and 31 patients were in severe OSAS group. Bilateral CIMT assesment and PWV analysis were performed in patients and controls.*

Results: *Significant differences existed between control subjects and patients with mild, moderate and severe OSAS in PWV (5.70±0.48, 6.76±0.61, 7.72±0.82, 8.94±1.72 m/sec respecitively; p<0.0001) and CIMT (0.712±0.040, 0.812±0.037, 0.900±0.056, 0.971±0.74 mm respectively; p<0.0001). AHI and TST% were positively correlated with the following; the PWV (p<0.001- r=0.67 / p<0.001- r=0,70 respectively), the maximal CIMT (p<0.001- r=0.79 / p<0.001- r=0.74 respectively), The minimal SaO_2 values were negatively correlated with the following; the PWV (p<0.001, r=-0.66), the maximal CIMT (p<0.001, r=-0.68).*

Conclusion: *OSAS patients have tendency to atherosclerosis development, and this process increases proportionally with the severity of the disease.*

Key Words: *Obstructive sleep apnea, pulse wave analiysis, carotid intima-media thickness, atherosclerosis*

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ATEROSKLEROTİK RİSK FAKTÖRLERİ OLMAYAN OBSTRÜKTİF UYKU APNE SENDROMLU HASTALARDA SUBKLİNİK ATEROSKLEROZUN SAPTANMASI

ÖZET

Amaç: Obstrüktif uyku apne sendromunda (OSAS) kardiyovasküler morbidite ve mortalite artmıştır. Son çalışmalarda OSAS ile karotis intima-media kalınlığı (CIMT) ve nabız dalga hızı (PWV) ölçümü ile erken dönemde belirlenebilen ateroskleroz arasında patofizyolojik bağlantı olduğu gösterilmiştir. Bu çalışmanın amacı bilinen kardiyovasküler hastalığı veya aterosklerotik risk faktörü olmayan OSAS'lı hastalarda subklinik ateroskleroz varlığını saptamak ve hastalığın ciddiyeti ile ilişkisini araştırmaktır.

Materyal ve Metod: Bilinen kardiyovasküler hastalığı veya aterosklerotik risk faktörü olmayan 30 hafif, 32 orta ve 31 ciddi OSAS'lı hasta ile bilinen herhangi bir sistemik hastalığı ve OSAS'ı olmayan 31 kontrol hastası çalışmaya alındı. Hasta ve kontrol gruplarında bilateral CIMT ve PWV ölçümü yapıldı.

Bulgular: Kontrol grubu ile hafif, orta ve ciddi OSAS'lı hastalar karşılaştırıldığında PWV (5,70±0,48; 6,76±0,61; 7,72±0,82; 8,94±1,72 m/sn sırasıyla; p<0,0001) ve CIMT (0,712±0,040, 0,812±0,037; 0,900±0,056; 0,971±0,74 mm sırasıyla; p<0,0001) değerlerinde anlamlı farklılık saptandı. Korelasyon analizinde; AHİ ve %TST ile PWV (p<0,001- r=0,67 / p<0,001- r=0,70 sırasıyla) ve maksimum CIMT (p<0,001- r=0,79 / p<0,001- r=0,74, sırasıyla) arasında pozitif korelasyon saptandı. En düşük SaO_2 ile PWV (p<0,001, r=-0,66) ve maksimum CIMT (p<0,001, r=-0,68) değerleri arasında negatif korelasyon saptandı.

Sonuç: OSAS'lı hastalarda ateroskleroz gelişim riski artmıştır ve bu risk artışı hastalığın ciddiyetindeki artış ile doğru orantılı olarak artmaktadır.

Anahtar Kelimeler: Obstrüktif uyku apne, nabız dalga analizi, karotis intima-media kalınlığı, ateroskleroz

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INTRODUCTION

Obstructive sleep apnea (OSAS) is characterized by repetitive apnea or hypopnea due to narrowing of the upper airways during sleep. It is a common disorder of middle-aged adults, affecting 4% of men and 2% of women.[1] OSAS is an independent risk factor for cardiac mortality and morbidity. In patients without underlying cardiovascular disease, hypertension, coronary artery disease, stroke, and heart failure are shown to be associated with OSAS. These conditions are independent risk factors for cardiovascular morbidity and mortality and OSAS participates in the genesis of these conditions.[2,3] Recent studies have indicated that OSAS is associated with multiple causal factors of endothelial damage and atherosclerosis. Systemic inflammation, oxidative stress, increased levels of soluble adhesion molecules and coagulation factors seem to be responsible for this relationship. Furthermore, all of these factors have been reported to significantly decrease after treatment with continuous positive airway pressure.[4,5]

Atherosclerosis is a process which is characterized by vessel wall remodeling that occurs over years. Obesity, aging, hypertension, diabetes, and hyperlipidemia have a major impact on the progression of atherosclerosis. Age, hypertension, hyperlipidemia and obesity are common risk factors for both atherosclerosis and OSAS. In recent studies there is an evolving evidence that OSAS is an independent factor for development of atherosclerosis.[3]

Carotid intima-media thickness (CIMT), flow-mediated dilation (FMD) and pulse wave velocity (PWV) measurement methods are used to determine subclinical atherosclerosis in OSAS.[6] Endothelial dysfunction is a marker of vascular damage before development of atherosclerotic plaques. Inhibition of nitric oxide (NO) synthesis by chemical or mechanical stimulation, or inhibiton of vascular response to NO are responsible mechanisms for endothelial dysfunction. Endothelial injury results in reduced arterial elasticity and increased arterial stiffness. Arterial stiffness is assessed by the degree of increase in PWV. Previous studies demonstrated that increased arterial stiffness is a marker of increased cardiovascular mortality and morbidity.[7,8] CIMT increasement develops as a result of intimal smooth muscle proliferation and accumulation of atherogenic particles. CIMT can be used in early diagnosis of atherosclerosis, risk classification and evaluation of response to treatment.[9]

The aim of this study was to investigate the presence of early signs of atherosclerosis in OSAS patients and correlation of these parameters with severity of the disease. In our study we excluded the patients with traditional risk factors for atherosclerosis, including hypertension, smoking, diabetes and hyperlipidemia.

We evaluated the early signs of atherosclerosis with the PWV and CIMT measurement methods in OSAS patients without any treatment for OSAS. →

MATERIAL and METHOD

Patients

Patients between ages 30 and 60 years with OSAS diagnosis who were examined in department of Chest Diseases outpatient clinic between dates March 2009 and October 2010 were included in this study after conducting polysomnographies at the sleep laboratory. According to the severity which was determined by the AHI (apnea-hypopnea index), patients were examined in three groups; 30 patients in mild OSAS (AHI=5-15), 32 patients in moderate (AHI=16-30) OSAS and 31 patients in severe (AHI>30) OSAS group. As a control group, we chose 31 asymptomatic healthy individuals aging between 30 and 60 years without cardiovascular diseases who visited department of cardiology outpatient clinic for cardiovascular check-up. The healthy group used in the study included patients suitable for the study from the perspective of cardiac anatomy and functions, those with no night snoring or day-time sleepiness, who scored less than 10 in the Epworth sleepiness scale, and had low risk of OSAS in the Berlin survey form evaluation.[10-12] The study was approved by the local Ethics Committee. Informed consents have taken from every individual included in the study. All patients underwent a detailed examination of the cardiovascular system. Biochemical parameters were obtained from venous blood samples drawn after a 8 hour fasting period.

Criteria for Exclusion

Exclusion criteria were as follows: (1) impaired cardiopulmonary function, defined as the occurrence of respiratory failure, pulmonary infection or congestive heart failure; (2) coronary artery disease, defined as having a typical angina pectoris, history of a prior myocardial infarction, presence of a positive stress test or positive coronary angiographic findings; (3) valvular disease, atrial fibrillation or congenital heart disease; (4) hypertension, diabetes, dyslipidemia (LDL cholesterol >160 mg/dl, total cholesterol >240 mg/dl, triglyceride >250 mg/dl), using antihypertensives, antidiabetics and lipid-lowering treatment; (5) chronic alcoholism and smoking; (6) malignancy; (7) history of prolonged use of non-steroid anti-inflammatory drugs or anticoagulants; (8) renal and liver insufficiency.

Polysomnography

Polysomnography was performed with 16 channels Embla (Medcare Inc, Iceland) with a continuous monitoring of a sleep technician. The system consists of 4 channels of EEG, 2 channels of EOG, submental EMG, oronasal air flow, thoracic and abdominal movements, pulse oximeter oxygen saturation, tibial EMG, body position detector, electrocardiogram and tracheal sound. Apnea was defined as complete stopping of airflow lasting more than 10 seconds. Hypopnea was defined as 30% or more reduction in respiratory airflow lasting more than 10 seconds and it is accompanied with a decrease of ≥4% in oxygen saturation. The average number of episodes of apnea and hypopnea per hour of sleep were defined as apnea hypopnea index (AHI). According to the severity, included patients were classified as mild OSAS (AHI=5-15), moderate OSAS (AHI=16-30) and severe OSAS (AHI>30). Sleep stages were scored following standard criteria with 30-s epochs and were reviewed and verified by a certified sleep physician.[13]

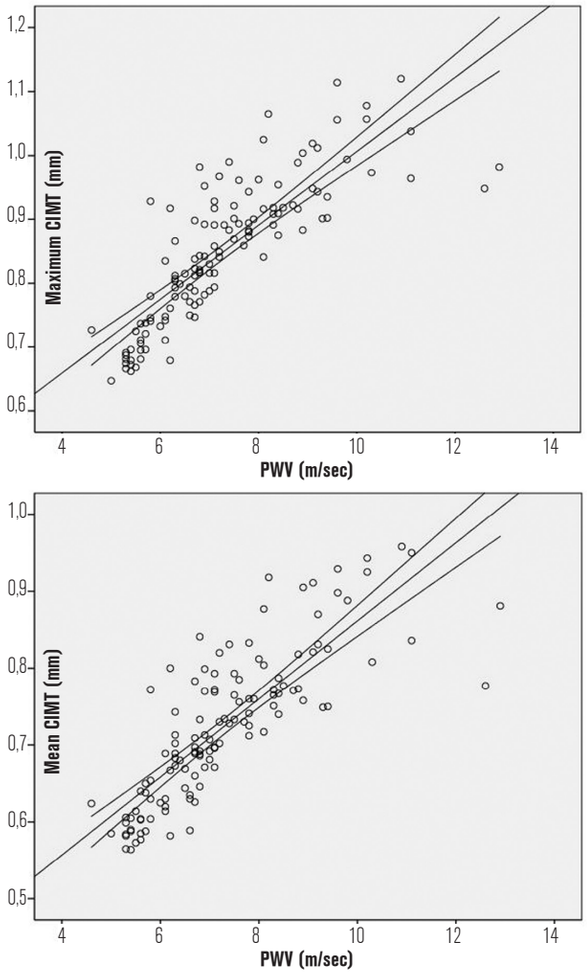

Figure 1: Corelation between maximum carotid intima-media thickness (Maximum CIMT), mean carotid intima-media thickness (Mean CIMT) and pulse wave velocity (PWV)

Pulse Wave Velocity and Carotid Intima-Media Thickness Measurement

CIMT measurements of the individuals were performed by a physician blinded to both patient and the obtained→

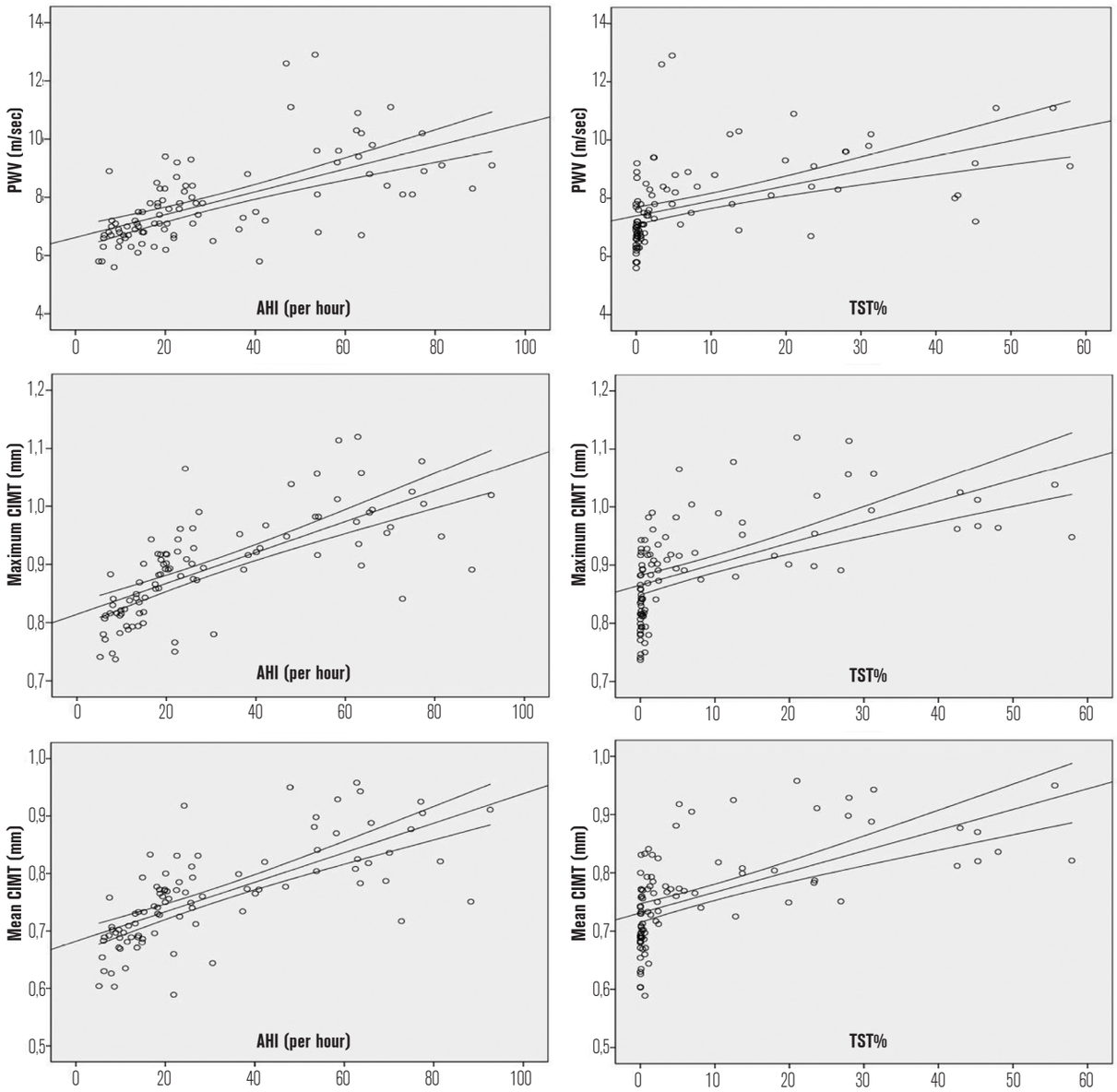

Figure 2: Corelation between pulse wave velocity (PWV), maximum carotid intima-media thickness (Maximum CIMT) , mean carotid intima-media thickness (Mean CIMT) and apnea hypopnea index (AHI), percentage of recording time spent at a oxygen saturation <90% [SaO_2 < 90% (TST%)].

PWV value. Both common carotid arteries were visualized by Toshiba Powervision 7500 (Toshiba AG) ultrasound device with a 7.5 MHz linear probe. Maximum and mean thicknesses were calculated with the far edge measurement method by the CIMT measurement program M'ATH® standart version 2.0.1.0 (Metris AG, France) from a determined 1 cm segment of common carotid artery, 2-3 cm distal to bulbus. This method was applied for the measurement of both common carotid arteries were evaluated based on the average.

For the measurement of PWV, SphygmoCor (Artcore, Sydney, Australia) device was used. Before the procedure, blood pressures were measured in patients. Distance between the palpable point of femoral artery and sternal notch and the distance between the most distal palpable part of carotid pulse and sternal notch were recorded to system. Applanation tonometry of the device was applied through the skin to these points sequentially. Recording was done after the most appropriate waveform amplitude and shape were obtained. Simultaneous ECG records were taken from patients. Pulse transit time, in other words pulse wave velocity (PWV) were calculated automatically by the SphygmoCor device by subtracting the time between the ECG and proximal pulse from the time between the ECG and distal pulse

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Statistical Analysis

All data were analyzed with "MedCalc 11.0.4" and "SPSS 15.0 for Windows" software. Numerical →

variables were defined as mean ± standart deviation, categorical variables were defined as percentiles. In comparision of three or more groups, if the variables fit the normal distribution, the one way ANOVA test; if not, the Kruskal Wallis test was used. In comparision of the categorical variables multiple comparision Chi Square test was used. In post-hoc analysis Tukey test was used after one way ANOVA test, and Mann Whitney U test was used after Kruskal Wallis test. Kolmogorov-Smirnov test was used in testing for normality of the distribution. Spearman correlation analysis performed for the determination of correlation. All hypotheses were established as two-way, and alpha critical value was accepted as 0.05.

RESULTS

Basic Characteristics of the Patients and Controls

There were no difference among groups in terms of demographic data; age, sex, body mass index, systolic and diastolic blood pressures, and in laboratory parameters; fasting blood glucose, HbA1c, serum lipid parameters (Table 1).

The mean AHI in mild OSAS patient group was 10.3±3, in moderate OSAS patient group it was 21.5±3.5, and in severe OSAS patient group it was 59.4±15.9. The difference in AHI among groups was statistically significant. Minimal oxygen saturation (min-SaO_2) and the percentage of recording time spent at a SaO_2 less than 90% [SaO_2<90% (TST%)] were different among groups with statistical significance (Table 1).

Pulse Wave Velocity and Carotid Intima-Media Thickness

The PWV and the CIMT values of OSAS patients were higher than the normal healthy individuals (p<0.0001). The PWV and CIMT values showed a proportional increase correlated with the disease severity (p<0.0001) (Table 2).

With the increase of the PWV values, the maximal and mean CIMT values were found to be increasing (p<0.001, r=0.88 and p<0.001, r=0.86) (Figure 1). The AHI and TST% were a positively correlated with the following; the PWV (p<0.001- r=0.67 / p<0.001- r=0.70, respectively), the maximal CIMT (p<0.001- r=0.79 / p<0.001- r=0.74, respectively), and the mean CIMT (p<0.001- r=0.77 / p<0.001- r=0.72, respectively) (Figure 2). The min-SaO_2 values were negatively correlated with the following; the PWV (p<0.001, r=-0.66), the maximal CIMT (p<0.001, r=-0.68), and the mean CIMT (p<0.001, r=-0.65) (Figure 3).

Table 1: Baseline characteristcs in control group and OSAS subgroups

	Control group (mean±sd) (n=31)	Mild OSAS (mean±sd) (n=30)	Moderate OSAS (mean±sd) (n=32)	Severe OSAS (mean±sd) (n=31)	p value
Age (years)	46.7±8.4	46.1±8.2	48.3±7.6	47.3±7.7	0.71
BMI (kg/m^2)	28.9±2.9	28.4±3.1	28.7±2.7	29.2±2.9	0.77
SBP (mmHg)	119.8±8.8	119.1±6.7	121.7±6.7	121.6±8.9	0.49
DBP (mmHg)	73.7±6.0	73.8±5	74.7±5	75.8±5	0.77
Fasting blood glucose (mg/dl)	89.4±8.2	89.8±8.6	91.7±10.5	92.5±9.4	0.49
HbA1c (%)	5.5±0.4	5.6±0.2	5.6±0.4	5.6±0.4	0.78
Total cholesterol (mg/dl)	191.3±23.8	188.7±33.1	190.5±43.1	195.6±26.4	0.86
LDL cholesterol (mg/dl)	117.5±23.5	113±33.9	119.7±35.9	119.8±30.6	0.81
HDL cholesterol (mg/dl)	46.8±10.8	44.9±13.6	44.2±10	45.2±10.4	0.83
Triglyceride (mg/dl)	146±67.9	144.6±57.9	148.4±81.7	149.5±50.8	0.99
AHI		10.3±3	21.5±3.5	59.4±15.9	<0.0001
SaO_2 min		87.3±3.6	83.2±4.8	71.4±10	<0.0001
SaO_2<90% (TST%)		0.22±0.34	3.9±8.2	20.5±17.3	<0.0001

OSAS: Obstructive sleep apnea syndrome, mean ± sd: mean ± standart deviation, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, AHI: Apnea-hypopnea index, SaO_2 min: Minimal oxygen saturation, TST: Total sleep time, SaO_2<90% (TST%): Percentage of recording time spent at a SaO_2<90%

Table 2: Comparision of groups in terms of carotis intima media thickness and pulse wave velocity

	Control group (mean±sd)	Mild OSAS (mean±sd)	Moderate OSAS (mean±sd)	Severe OSAS (mean±sd)	p value
PWV (m/sec)	5.70±0.48	6.76±0.61	7.72±0.82	8.94±1.72	<0.0001
Maximum CIMT (mm)	0.712±0.040	0.812±0.037	0.900±0.056	0.971±0.074	<0.0001
Mean CIMT (mm)	0.615±0.037	0.686±0.040	0.761±0.056	0.833±0.075	<0.0001

Mean ± sd: mean ± standart deviation, PWV: Pulse wave velocity, CIMT: Carotid intima media thickness, OSAS: obstrucvtive sleep apnea syndrome

DISCUSSION

OSAS is a systemic disorder and leads to cardiovascular complications.[14] Recent studies showed that OSAS is not a simple respiratory abnormality during sleep, with the systemic inflammatory response it seems to be associated with cardiovascular diseases and increased atherosclerotic process. OSAS may be associated with the hypertension, diabetes mellitus and hyperlipidemia which increase the risk of atherosclerosis. In OSAS, hypoxia and intermittant reoxygenation episodes result with the oxidative stress which leads to endothelial dysfunction and increased symphatetic tone.[14,15]

Atherosclerosis is a progressive inflammatory process which results with fatal vascular events.[16] Endothelial injury is the initial mechanism that triggers the atherosclerotic process. OSAS is more prevalent in patients with hypertension, diabetes mellitus, obesity, coronary artery disease, stroke and heart failure, in which the endothelial dysfunction plays a key role.[15] Recent studies have shown the presence of the endothelial dysfunction in OSAS. It has been shown →

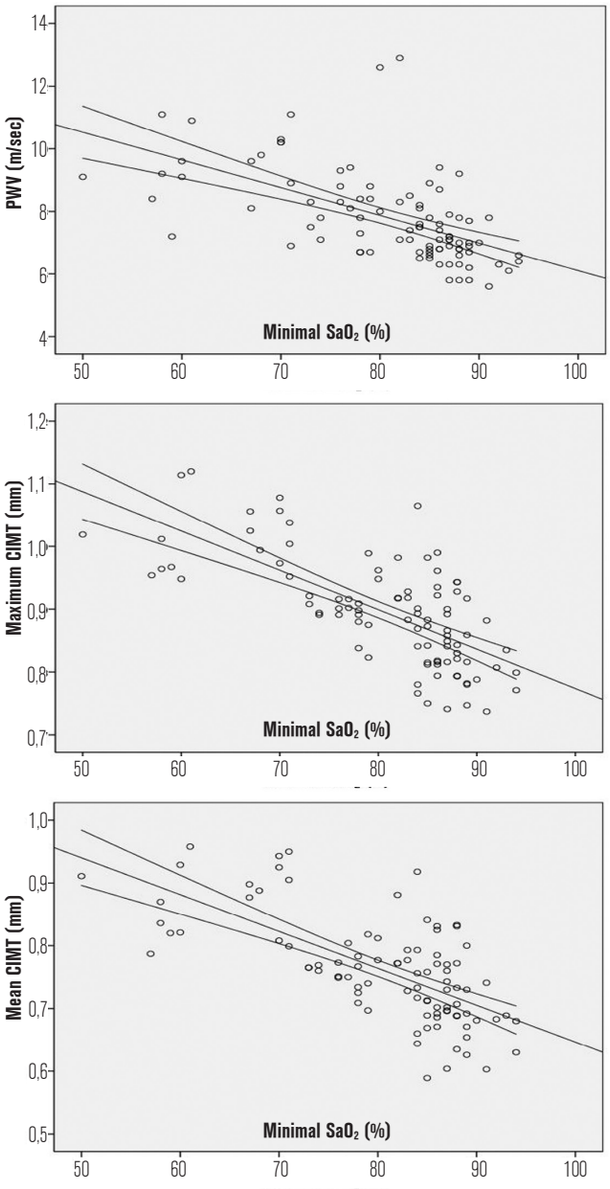

Figure 3: Corelation between minimal oxygen saturation (Minimal SaO_2) and pulse wave velocity (PWV), maximum carotid intima-media thickness (Maximum CIMT) and mean carotid intima-media thickness (Mean CIMT).

that various proinflammatory and prothrombotic factors in OSAS.[14,15] Serum CRP, fibrinogen, IL-6 levels and insulin resistance were shown to be increased in OSAS patients. Nasal CPAP (continous positive airway pressure) therapy have shown to decrease CRP, IL-6 levels and insulin resistance.[5] Many of the studies investigating the cardiovascular morbidity and mortality in OSAS patients were cross sectional, retrospective or with a short term observation interval. Another important point of those studies was the coincidence of OSAS with the situations (obesity, hypertension and etc.) which have a role in atherosclerosis development. Because of this there is a suspicion in the causal relationship of OSAS with the cardiovascular diseases.[17]

There were many studies investigated the relationship of OSAS with the atherosclerosis. Initially CIMT measurement method was used to determine the subclinical atherosclerosis, afterwards the PWV measurement method was used in establishment of increased arterial wall stiffness.[18]

In our study, the relationship of OSAS with subclinical atherosclerosis were investigated in individuals aging between 30 and 60 years and without both proven atherosclerosis and the risk factors which have a role in atherosclerosis development, who were diagnosed as OSAS with the polysomnography test. The OSAS patients were examined in three different groups according to severity of the disease, and the correlation of the PWV and CIMT values with the severity of the disease was investigated.

There were studies showed that the CIMT increases in OSAS compared with normal individuals. In a study of Li Chong et al. the CIMT values found to be increased in patients with mild, moderate and severe OSAS compared with the healthy indiviudals. In the same study, the CIMT values of moderate and severe OSAS patients were found higher than the mild OSAS patients and there were no difference found between patients with moderate and severe OSAS in terms of CIMT.[19] Altın et al. found that the CIMT values of severe OSAS patients were higher than the mild OSAS patients and normal healthy individuals with statistical significance.[20] Minoguchi et al. found that the the CIMT values of OSAS patients were found higher than the obese control patients.[21] In another study which examined 130 OSAS patients, the CIMT and PWV values were not found to be correlated with the disease severity.[18] Tanriverdi et al. examined subclinical atherosclerosis with the flow mediated dilatation method (FMD) and CIMT, and they found that in OSAS patients the CIMT was higher and FMD was lower with a statistical significance. Also they found a correlation between the FMD and the disease severity.[6]

In some of those studies the OSAS patients were only compared with normal healthy individuals. Only in a small number of studies the OSAS patients were classified according to the severity, but in those the patients with coincident risk factors for atherosclerosis were not excluded. In our study, we excluded the patients with risk factors for atherosclerosis and we stratified the patients according to their severity. In majority of the previous reports CIMT values were found higher in OSAS patients when compared with healthy individuals, however, contradictory results exist about the relationship between this increase with the severity of the disease. In our study the CIMT was higher in OSAS patients than the healthy individuals→

and there was a relationship between the disease severity and the increased CIMT values. The AHI and the percentage of recording time spent at a SaO_2<90% (TST %) parameters which show the disease severity were found to be positively correlated with the increased CIMT. The min-SaO_2 was found to be negatively correlated with the CIMT.

The compliance of the arterial system has a major impact on the cardiovascular system.[22,23] In many studies, the arterial stiffness had been shown to be an independent predictor of cardiovascular morbidity and mortality.[23-26] The direct measurement of vascular compliance is difficult. PWV analysis method enables us to determine arterial compliance noninvasively. The PWV is negatively correlated with the arterial elasticity. In many studies, the relationship between the atherosclerotisis and the changes in PWV had been shown previously.[22,23,26,27] It is known that, as a reflection of arterial stiffness, the increased PWV, is known to be an indicator of atherosclerosis.[26]

In study of Nagahama et al., the OSAS patients without exclusion of atherosclerotic risk factors, were compared with normal healty controls with PWV method. Ankle-brachial PWV was found to be greater in OSAS patients than controls. For the exclusion of hypertensive individuals, OSAS patients still had greater PWV than the normal individuals significantly.[28] Drager et al. found that, the CIMT and PWV were significantly greater in severe OSAS patients than the mild and moderate OSAS patients, however there were no any statistically significant difference between mild and moderate OSAS patients and healthy individuals. Besides this, the PWV was found to be correlated with AHI, min-SaO_2, and TST %; whereas CIMT was only correlated with the AHI.[3]

Also in our study the carotid-femoral PWV was found greater in OSAS patients than controls with a statistical significance. As similar to the CIMT, the increase in PWV was related with the disease severity. Both the AHI and TST % were a positively correlated with the PWV. In addition there was a negative correlation between the PWV and min-SaO_2.

In our study we found that, the PWV and the mean and maximum CIMT were increased in patients with OSAS. Also, by comparing the OSAS patients among themselves; we found that, both PWV and CIMT increased along with the disease severity. At the same time we found a significant correlation between the PWV and CIMT values.

This study shows us that, even if there were no any coincidental risk factors for atherosclerosis, the OSAS patients had increased PWV and CIMT values which denote the atherosclerosis development. This increase in PWV and CIMT correlated with the disease severity which means that the atherosclerosis development increased along with the disease severity.

One limitation of our study was using the method of Epworth and Berlin scale rather than the PSG, in the selection of control individuals. However in daily clinical practice, we use those methods for the selection of appropriate patients for the polysomnography test.

In conclusion, early signs of atherosclerosis are present in OSAS patients, and these findings are correlated with the OSAS severity. This supports the hypothesis that, OSAS has an independent role in atherosclerosis progression. As a result of these reasons, in these patients, screening for cardiovascular diseases is important for the prevention of cardiovascular mortality and morbidity. The patients with increased CIMT and PWV have to be identified, and because of the high risk for atherosclerosis development in these patients, treatment should be initiated in the early stage. We think that, these significant findings of our analysis can guide for the further clinical practice. However these findings must be supported clinically with prospective cohort studies.

Conflict of interest: None declared

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REFERENCES

1. Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993; 328: 1230-1235.
2. Lattimore JD, Celermajer DS, Wilcox I. Obstructive sleep apnea and cardiovascular disease. J Am Coll Cardiol 2003; 41: 1429-1437.
3. Drager LF, Bortolotto LA, Lorenzi MC, et al. Early Signs of Atherosclerosis in Obstructive Sleep Apnea. Am J Respir Crit Care Med 2005; 172: 613-618.
4. Ryan S, Taylor CT, McNicholas WT. Systemic inflammation: a key factor in the pathogenesis of cardiovascular complications in obstructive sleep apnoea syndrome? Thorax 2009; 64: 631-636.
5. Yokoe T, Minoguchi K, Matsuo H. Elevated Levels of C-Reactive Protein and Interleukin-6 in Patients With Obstructive Sleep Apnea Syndrome Are Decreased by Nasal Continuous Positive Airway Pressure. Circulation 2003; 107: 1129-1134.
6. Tanriverdi H, Evrengul H, Kara CO, et al. Aortic stiffness, flow-mediated dilaation and carotid intima-media thickness in obstructive sleep apnea. Respiration 2006; 73: 741-750.
7. Wright CI, Brouwer-de Cock KA, Kroner CI, et al. The relation on arterial stiffness to endothelial function in healthy subjects. Physiol

Meas 2007; 28: 573-582.
8. Duprez DA, Cohn JN. Arterial stiffness as a risk factor for coronary atherosclerosis. Curr Atheroscler Rep 2007; 9: 139-144.
9. Mukherjee D, Yadav JS. Carotid artery intima-medial thickness: indicator of atherosclerotic burden and response to risk factor modification. Am Heart J 2002; 144: 753-759.
10. Netzer NC, Stoohs RA, Netzer CM, et al. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med 1999; 131: 485-491.
11. Manni R, Politini L, Ratti MT, et al. Sleepiness in obstructive sleep apnea syndrome and simple snoring evaluated by the Epworth Sleepiness Scale. J Sleep Res 1999; 8: 319-320.
12. Grover M, Mookadam M, Armas D, et al. Identifying patients at risk for obstructive sleep apnea in a primary care practice. J Am Board Fam Med 2011; 24: 152-160.
13. Iber C, Ancoli-Israel S, Chesson A, Quan SF, editors. 1st ed. Westchester, IL: American Academy of Sleep Medicine; 2007. The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specification.
14. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/american College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Circulation 2008; 118; 1080-111.
15. Pack AI, Gislason T. Obstructive sleep apnea and cardiovascular disease: a perspective and future directions. Prog Cardiovasc Dis 2009; 51: 434-451.
16. Libby P. Inflammation in atherosclerosis. Nature 2002; 420: 868-874.
17. Wright J, Johns R, Watt I, et al. Health effects of obstructive sleep apnea and the effectiveness of continuous positive airway pressure: a systematic review of the research evidence. BMJ 1997; 314: 851-860.
18. Baguet JP, Nadra M, Barone-Rochette G, et al. Early cardiovascular abnormalities in newly diagnosed obstructive sleep apnea. Vascular Health and Risk Management 2009; 5: 1063-1073.
19. Li C, Zhang X, Liu H, et al. Association among plasma interleukin-18 levels, carotid intimamedia thickness and severity of obstructive sleep apnea. Chin Med J 2009; 122: 24-29.
20. Altın R, Özdemir H, Mahmutyazıcıoğlu K, et al. Evaluation of carotid artery wall thickness with high-resolution sonography in obstructive sleep apnea syndrome. J Clin Ultrasound 2005; 33: 80-86.
21. Minoguchi K, Yokoe T, Tazaki T, et al. Increased carotid intima-media thickness and serum inflammatory markers in obstructive sleep apnea. Am J Respir Care Med 2005; 172: 625-630.
22. Bortolotto LA, Safar ME, Billaud E, et al. Plasma homocysteine, aortic stiffness, and renal function in hypertensive patients. Hypertension 1999; 34: 837-842.
23. Blacher J, Asmar R, Djane S, et al. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. Hypertension 1999; 33: 1111-1117.
24. Asmar R, Rudnichi A, Blacher J, et al. Pulse pressure and aortic pulse wave are markers of cardiovascular risk in hypertensive populations. Am J Hypertens 2001; 14: 91-97.
25. Blacher J, Pannier B, Guerin AP, et al. Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end-stage renal disease. Hypertension 1998; 32: 570-574.
26. Van Popele NM, Grobbee DE, Bots ML, et al. Association between arterial stiffness and atherosclerosis: the Rotterdam Study. Stroke 2001; 32: 454-460.
27. Asmar R, Benetos A, Topouchian J, et al. Assessment of arterial distensibility by automatic pulse wave velocity measurement: validation and clinical application studies. Hypertension 1995; 26: 485-490.
28. Nagahama H, Soejima M, Uenomachi H, et al. Pulse Wave Velocity as an Indicator of Athrosclerosis in Obstructive Sleep Apnea Syndrome Patients. Internal Med 2004; 43: 184-188.