

Tıkayıcı uyku apne sendromlu hastalarda boyun ve bel çevresi arteriyel intima media kalınlığının bir göstergesi olabilir mi?

Can the circumferences of neck and waist be as a predictor of arterial intima media thickness in the patients with obstructive sleep apnea syndrome?

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ÖZ

GİRİŞ ve AMAÇ: Karotid ve femoral arter intima media kalınlığı (İMK), vücut kitle indeksi (VKİ) ölçümleri kardiyometabolik risk belirteçleridir. Literatürde tıkayıcı uyku apneli (TUA) hastalarında bu belirteçler tek tek ele alınmış fakat boyun ve bel çevresinin bölgelerindeki arter kalınlıkları üzerinde etkisini inceleyen bir çalışma yapılmamıştır. Çalışmamızın amacı; varsa bu ilişkiyi ortaya koymak ve olası sebeplerini irdelemektir.

YÖNTEM ve GEREÇLER: Çalışmamıza toplam 195 hasta ve 50 kontrol hastası alındı. Hastalardan sigara içme, apne, inme, anjina pectoris, kronik böbrek hastalığı, diyabet öyküsü olanlar ve 65 yaş üstü olanlar çalışmadan dışlandılar. Sonografik İMK ölçümleri, yüksek çözünürlüklü B- mod Ultrason (Philips EPIQ 7) nin lineer probu (8–12 MHz) ile yapıldı. KİMK ölçümleri; sağ arteria carotis communisin posteromedial duvarından, karotid bulbusun 1-3 cm distalinden, plak bulunmayan üç noktadan alındı. Femoral arter İMK ölçümleri de sağ ana femoral arterin arka duvarından ölçüldü. Her iki grupta boyun ve bel çevresi de ölçülüp ayrıca VKİ hesaplandı.

BULGULAR: TUA grubunda kontrol grubuna kıyasla KİMK, VKİ, boyun çevresi ve bel çevresi ortalamaları yüksek ve istatistiksel olarak anlamlıyken, fİMK değerlerinde fark yoktu. TUA grubunda boyun çevresi ile KİMK ölçümleri arasında pozitif yönlü doğrusal bir ilişki varken, bel çevresi ve fİMK arasında bir ilişki yoktu.

TARTIŞMA ve SONUÇ: TUA hastalarının erken değerlendirilmesi, bu hastalığın kardiyovasküler ve serebrovasküler hastalıklar için bağımsız bir risk faktörü olmasından dolayı önemlidir. Bu hastalıklar için öncül olarak kabul edilen karotis İMT kalınlaşmasının, boyun çevresi ve VKİnin zamanında ölçümü gerekli önlemleri almak için zaman sağlayabilir. Ayrıca sadece boyun çevresi ölçümü bile KİMK hakkında bilgi verebilir.

Anahtar Kelimeler: karotis intima media kalınlığı, femoral intima media kalınlığı, tıkayıcı uyku apne sendromu, boyun çevresi, bel çevresi

ABSTRACT

INTRODUCTION: Carotid and femoral artery intima media thickness (cIMT and fIMT) and body mass index (BMI) have been studied individually in patients with obstructive sleep apnea syndrome (OSAS). But no studies have examined the effect of the neck and waist circumference (NC and WC) on arterial IMT in their region. The aim of our study; to reveal this relationship and the possible causes.

METHODS: A total of 245 study subjects were included in the study. Patients with a history of smoking, apnea, stroke, angina pectoris, chronic kidney disease, diabetes and those over 65 years of age were excluded from the study. Sonographic IMT measurements were performed with B-mode Ultrasound (Philips EPIQ 7). CİMT measurements were taken from the posteromedial wall of the right common carotid artery. FİMT measurements were also measured from the posterior wall of the right main femoral artery. NC and WC were measured and BMI was calculated in both groups.

RESULTS: The mean cIMT, BMI, NC and WC were significantly higher in the OSAS group, but there was no difference in the fİMT values. In the OSAS group, there was a positive linear correlation between NC and cIMT measurements, whereas there was no correlation between WC and fİMT.

DISCUSSION AND CONCLUSION: Early evaluation of OSAS patients is beneficial because it is an independent risk factor for cardiovascular and cerebrovascular diseases. Timely measurements of cIMT, NC and BMI may provide time for taking necessary measures for these diseases. In addition, even the NC measurement can provide information about cIMT.

Keywords: carotid intima media thickness, femoral intima media thickness, obstructive sleep apnea syndrome, neck circumference, waist circumference

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INTRODUCTION

The prevalence of OSAS increases 2-3 fold due to physiological changes related to aging. OSAS occurs in approximately 4% of men and 2% of women aged 30-60. This disease is characterized by increased respiratory effort, sleep disruption and nocturnal intermittent hypoxia. For the diagnosis of OSAS, at least 5 apnea events per hour should occur, accompanied by clinical symptoms such as daytime sleepiness (1, 2). Risk factors for OSAS include male gender, age, alcohol consumption, cigarette smoking, overweight and obesity, large neck circumference, craniofacial abnormalities, physical inactivity and family history. The primary abnormality in patients with OSA is small pharyngeal airway an anatomically (1, 3).

OSAS is associated with increased sympathetic system activity, oxidative stress, vascular endothelial inflammatory mediators, platelet activation and hyperleptinemia, all of which can lead to vascular thickening (4, 5). OSA-associated oxygen desaturation and related apnea / hypopnea events support degenerative remodeling of the arterial wall and may be an early sign of subclinical atherosclerosis. Hypertrophic damage to the carotid artery caused by this remodeling appears to be related to the frequency and intensity of hypoxemia (6).

Intima media thickness (IMT) is a measure of the thickness of two wall layers of carotid or femoral artery, tunica intima and tunica media, a marker for identifying subclinical atherosclerosis and predicting cardiovascular risk. Early stage of cardiovascular disease can be evaluated with IMT, which is accepted as a sign of organ dysfunction of $\geq 0,75$ mm in humans (7, 8).

OSAS is difficult to evaluate as an independent risk factor for carotid artery atherosclerosis since patients with OSAS often also suffer from other risk factors such as obesity, hyperglycemia and hypercholesterolemia and insulin resistance etc. (5, 9, 10). In patients with OSAS, it was claimed that oscillating pressure waves generated during snoring can reach the carotid artery wall by neighboring tissues, and especially the carotid bifurcation adjacent to the lateral pharyngeal wall may be

exposed to these vibrations (11). Animal studies have also identified vibrations that accompany snoring in the carotid artery wall and lumen. These vibrating stimuli cause pathological damage to endothelial cells in the arterial wall, triggering inflammatory processes leading to early signs of atherosclerosis (12, 13, 14).

The aim of this study was to determine whether there is a relationship between cIMT and neck circumference, fIMT and waist circumference in the patients with OSAS. Additionally, this study was designed to investigate whether systemic and local causes that may cause vascular thickening have the same effect on both regions in the patients with OSAS.

MATERIALS AND METHODS

Participants

One hundred ninety-five patients with OSAS and fifty (50) control subjects from Adana City Research and Training Hospital Otorhinolaryngology and Chest Disease Clinics were included in this study. Patients with a history of smoking, stroke, angina pectoris, chronic kidney disease, diabetes, pregnancy, birth control medication, use of medications that may influence the hemostatic parameters and patients over 65 years of age were excluded from the study. All subjects gave signed informed consent form that provided a comprehensive description of the study. All procedures were approved by the Ethic Committee of Adana City Research and Training Hospital prior to initiation of this study.

Measurements

Physical measurements were performed when the participants applied for ultrasonic examination. Height and weight were measured when fasting and used to calculate body mass index (BMI) = weight / height² (kg / m²). Waist and neck circumference were measured at the top of iliac crest and cricoid level, respectively. Circumferences were measured while standing position with a flexible anthropometric tape that was not extensible, and each measurements were performed two or three times to obtain a consistent result.

OSAS diagnosis

The OSAS was diagnosed after a one night comprehensive diagnostic sleep studies that were performed at the sleep center of the Adana City and Research Hospital in a temperature-controlled and sound-attenuated room. Patients' body movements, electroencephalography, electromyography, heart and pulse changes with electrocardiography were recorded as measures of arousal from sleep. Nasal and oral airflow were recorded by thermistors. Oxygen saturation was measured by pulse oximetry. All PSGs were scored and read by a boarded physician who was unaware of the study and, therefore, blinded to the patients' participation in the study. The results of the sleep study were scored automatically, and subsequently reviewed to ensure accuracy of the data. The OSAS was diagnosed from a review of all data and the severity was quantified as the number of oxygen desaturations by more than 4% per hour of study. The OSAS diagnosis was made on the basis of an apnea/ hypopnea index (AHI) ≥ 5 per hour of electroencephalographic sleep. Central respiratory events were excluded from study.

Ultrasonography

Sonographic IMT measurements were performed by fifteen year experienced radiologist who was unaware of the clinical information of the patients with the linear probe of high resolution B-mode Ultrasound (Philips EPIQ 7) (8-12 MHz) in a supine position. For the CIMT and FIMT measurements, subjects were laid down for ten minutes in a quiet room. After this time, ultrasonic measurements were done to obtain and save ultrasound images of the carotid and femoral arteries for later analysis. For the CIMT measurement, the participant was instructed to lie in a supine position with the head slightly extended and turned to the left. For the femoral measurement, the participant was asked to lay their leg supine on the table while images were saved. CIMT measurements were taken from the posteromedial wall of the carotis communis, 1-3 cm distal from the carotid bulb, from three points without plaque at the right side. FIMT measurements were measured from the posterior wall of the right main

femoral artery. For both measurements, the regions were scanned with both longitudinal and transverse projections, in order to assess the occurrence of plaques. To assess intima-media thickness, lumen-intima and media-adventitia borders were observed as double lines on wall in longitudinal plane (Figure 1 and Figure 2). The ratio of mean CIMT to neck circumference, the ratio of mean FIMK to waist circumference were also calculated.

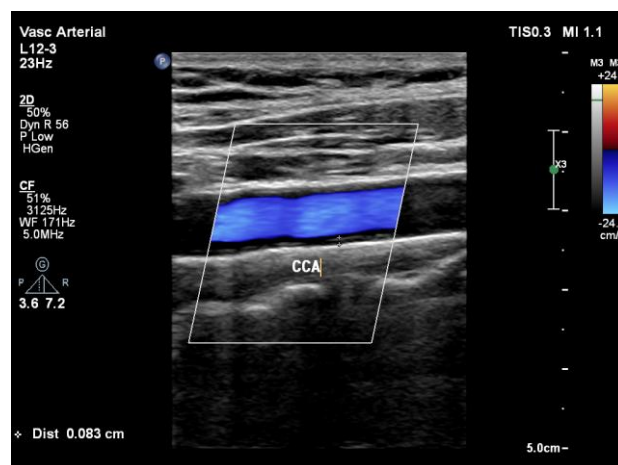


Figure 1. Measurement of intima-media thickness in OSAS patients (signed area indicates double lines that shows IMT)

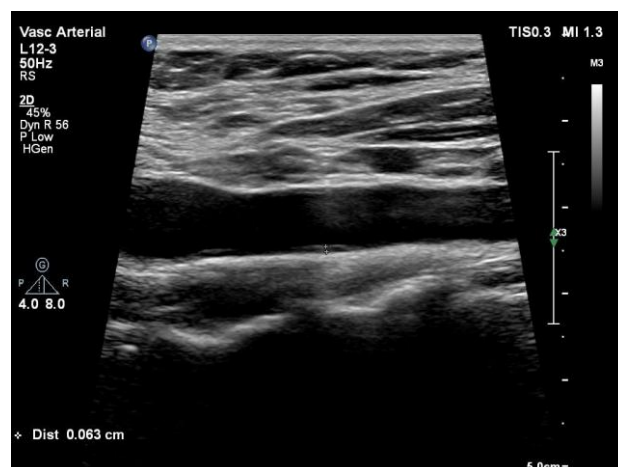


Figure 2. Intima-media thickness in normal subject (signed area shows IMT)

Statistical Analysis

Control of normality of continuous variables was performed by Shapiro Wilk test. Student's t test was used to compare the mean of continuous variables in groups with and without OSAS. Univariate Logistic Regression and Multivariate Logistic Methods were used to determine how many times the variables were found to be higher than those without OSAS problems. ROC method was used to

determine the cut-off point for OSAS of these variables and ROC curves were compared to show which variable was more effective in distinguishing OSAS. The distribution of gender according to the groups was analyzed by Chi-Square test. Statistical significance level was taken as 0.05 and SPSS 21 and MedCalc 16 demo version were used in the analyzes.

RESULTS

There was no significant difference between patient and control groups in terms of age and gender distribution ($p = 0.823$, $p = 0.483$, respectively). The mean cIMT, BMI, neck circumference and waist circumference were statistically higher in the OSA group compared to the control group, but there was no difference between the fIMT values ($p < 0.001$ for four, $p = 0.439$ for fIMT) (Table 1).

Table 1: Distribution of Patients and Findings by Groups			
	OSAS PATIENTS	CONTROL	P
Age	49,32±13,45	48,63±11,17	0,823
Gender			
Male, n (%)	157 (%80,5)	39 (%78,0)	0,483*
Female, n (%)	38 (%19,5)	11 (%22,0)	
cIMT (mm)	0,93±0,13	0,68±0,11	<0,001
fIMT (mm)	0,96±0,15	0,93±0,18	0,439
BMI (kg/m ²)	31,75±2,90	25,82±2,33	<0,001
NC (cm)	44,91±3,56	39,03±2,81	<0,001
WC (cm)	94,87±3,15	83,87±4,51	<0,001

p: Student's t Test, *Ki-Kare Test, OSAS: obstructive sleep apnea syndrome, cIMT: Carotid intima media thickness, fIMT: femoral intima media thickness, BMI: body mass index, NC: neck circumference, WC: waist circumference

There was a positive, moderately linear relationship between neck circumference and CIMENT measurements in OSAS group but not in the control group ($r=0,614$; $p < 0,001$ for OSAS and $r = -0,134$; $p = 0,170$ for control group). In general, there was a positive, moderately linear relationship between neck circumference and cIMT measurements ($r = 0,385$; $p < 0,001$). The relationship between neck circumference and CIMENT measurements varied between groups and was statistically significant ($p < 0,001$) (Table 2). There was no linear

relationship between waist circumference and fIMT in both groups ($r = -0,166$; $p = 0,173$ for OSAS, $r = -0,028$; $p = 0,443$ for control group). The relationship between waist circumference and fIMT did not change according to the groups ($p = 0,691$) (Table 2).

CIMT / neck circumference ratio was significantly higher in OSAS group compared to control group ($p < 0.001$). However, on the contrary, the fIMK / waist circumference ratio was significantly higher in the control group compared to the OSAS group ($p < 0.001$). (Table 3).

According to the multivariate analysis, all parameters except fIMK had a significant difference in the differentiation of OSAS (Table 4). Furthermore, when the areas under the curve were compared, the fIMK value was found to be significantly less distinctive than all other variables. In the distinction of OSAS, the area under the curve for cIMT was found to be 0.935 and the cut-off point was determined to be >0.77 mm. For fIMT, the area under the curve was found to be 0.571 and the cut-off point was determined to be >0.89 mm. The cut off point for neck and waist circumference was $>42,1$ cm and >86.9 cm respectively, and this rate was >29.3 for BMI (Figure 3).

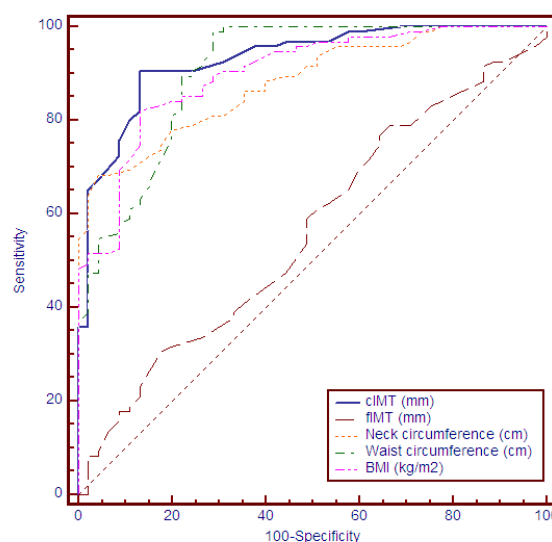


Figure 3. ROC curve of studied parameters for diagnosis of OSAS

Table 2: Correlation of neck circumference with carotid IMT and waist circumference with femoral IMT				
	OSAS PATIENTS	CONTROL	Total	
	cIMT (mm)	cIMT (mm)	cIMT (mm)	P
NC (cm)	r= 0,614;p<0,001	r= -0,134;p=0,170	r= 0,385 ;p<0,001	<0,001
	fIMT (mm)	fIMT (mm)	fIMT (mm)	
WC (cm)	r= -0,166;p=0,173	r= -0,028;p=0,443	r= -0,173;p=0,097	0,691

p: Significance of the Difference Between Two Correlation Coefficients (OSAS& Control)
 OSAS: obstructive sleep apnea syndrome, cIMT: Carotid intima media thickness, fIMT: femoral intima media thickness, NC: neck circumference, WC: waist circumference

Table 3: Distribution of carotid IMT / neck circumference ratio and femoral IMT / waist circumference ratio by groups			
Ratios	OSAS (Mean±SD)	Control (Mean ±SD)	p
cIMT (mm)/ NC (mm)	0,0227±0,00461	0,0171±0,00207	<0,001
fIMT (mm)/ WC (mm)	0,0103±0,00253	0,0142±0,00173	<0,001

p: Student's t Test, OSAS: obstructive sleep apnea syndrome, cIMT: Carotid intima media thickness, fIMT: femoral intima media thickness, NC: neck circumference, WC: waist circumference

Table 4: Multivariate analysis of all parameters					
	AUC (95% CI)	Sensitivity (95% CI)	Specificity(95% CI)	Cut off point	p
cIMT (mm)	0,935 (0,862 - 0,975)	90,54 (81,9 - 95,7)	87,71 (73,6 - 95,4)	>0,77	<0,001
fIMT (mm)	0,571 (0,482 - 0,639)	31,33 (22,6 - 42,4)	81,43 (66,2 - 91,8)	>0,89	0,243
NC (cm)	0,896 (0,807 - 0,945)	75,22 (61,5 - 87,3)	96,61 (83,1 - 99,6)	>42,1	<0,001
WC (cm)	0,898 (0,833 - 0,954)	94,54 (85,2 - 98,6)	72,27 (56,3 - 84,7)	>86,9	<0,001
BMI (kg/m2)	0,905 (0,823 - 0,945)	83,17 (71,5 - 90,1)	87,04 (72,6 - 95,2)	>29,3	<0,001

OSAS: obstructive sleep apnea syndrome, cIMT: Carotid intima media thickness, fIMT: femoral intima media thickness, BMI: body mass index, NC: neck circumference, WC: waist circumference

DISCUSSION

In our study cIMT, BMI, NC and WC were significantly higher in OSAS patients compared to normal control subjects. There was no difference in terms of fIMT. These results suggest that endothelium dysfunction of the carotid artery may be adversely affected by pericarotid tissue vibrations due to snoring, shear stress and local hemodynamics rather than a systemic disease (7, 15).

The pathophysiological mechanism linking snoring, OSAS and stroke are still unclear and remain widely unexplored. Many studies have shown IMT to be a risk factor for cardiovascular diseases and that there was a correlation between cIMT and OSAS (9, 15, 16).

Snoring generally occurs in 47,7% of men and 33,6% of women (17). Snoring is a risk factor for OSAS, some studies have investigated the association between snoring and risk for OSAS (12, 13, 18). Vibrations from snoring have been shown to be associated with causing endothelial dysfunction in the carotid artery. It has been shown in rabbits that vibration-induced endothelial dysfunction plays a crucial role in the early pathophysiological mechanism of atherosclerosis. This dysfunction can be detected by cIMT measurement in patients with sleep disorder (19, 20). In another rabbit study, it was shown that pericarotid vibration from snoring leads to endothelial dysfunction with increased cIMT (21). In experimental and population studies, snoring has been reported to induce atherosclerosis by creating vibrations in the carotid artery wall independent of OSAS (12, 22, 23, 24, 25, 26). Lee et al. (22) were objectively emphasized that snoring size correlated

with carotid atherosclerosis. Drager et al. (23) stated that snoring alone is not a risk factor and may be effective as part of OSAS. Lee et al. (24) responded that snoring induces carotid artery atherosclerosis independent of AHI and hypoxemia. Severe snoring was defined as an independent risk factor for carotid atherosclerosis in the absence of hypoxemia (22). Other authors concluded that IMT was found to be higher in snoring than non-snoring and mentioned that non-apneic snoring may be a precursor to IMT thickening (27). Young male habitual snorers had significantly greater cIMT compared with non-snorers, suggesting endothelial remodeling of the carotid artery in the another study (21). In our study, the presence of high cIMT and no change in fIMT was consistent with the findings in the literature suggesting there was a localized event as a cause in the neck like pericarotid vibrations.

In their study, Kaynak et al. (10) showed that carotid IMT was significantly higher in OSAS groups than in the control group. Previous studies have shown that OSAS may be important risk factors for the development of carotid atherosclerosis and stroke (28, 29). One study found that severe OSAS patients but without cardiovascular disease showed signs of early atherosclerosis with increased arterial stiffness and carotid remodeling (6). OSAS was an important risk factor for carotid artery atherosclerosis even in the exclusion of systemic diseases such as hypertension, hyperlipidemia, tobacco use and diabetes (9). In our study, concomitant diseases such as diabetes and cerebrovascular and cardiovascular diseases were excluded however, hypertension could not be excluded because hypertension is an expected consequence of OSAS. Altın et al. (30) found that carotid IMT of severe OSAS cases were significantly higher than those of mild OSAS and control cases. Silvestrini et al. (31) found that carotid IMT values in severe OSAS patients were significantly higher than the IMT values of the control group. OSAS is often a delayed diagnosis and this situation may have a very negative effect on the cardiovascular risk profile of patients, as confirmed by two studies (32, 33). In a newly diagnosed, non-smoker OSAS patients without a concomitant disease, IMT was

not found to be related with OSAS (34). Therefore, the assessment of early stages of atherosclerotic changes by intima-media thickness measurement appears to be a much better approach. Moreover, IMT assessment could be a valuable tool that is easy to detect in daily practice, repetitive and noninvasive. Contrary to the findings of these reports, Gorzewska et al. studied OSAS patients with no comorbidities, including hypertension, hyperlipidemia and diabetes. The authors demonstrated no significant differences in IMT between OSAS patients and healthy controls. They concluded that IMT does not reflect increased risk of cardiovascular events in OSAS patients with no coexisting disease (35). A cross-sectional study of a population of patients with recent ischemic cerebrovascular diseases showed also no association between self-reported snoring and carotid stenosis (36).

Since the prevalence of OSAS and cerebrovascular diseases increases with age, the choice of age groups of patients included in the study is important. In our study, the mean age of patients with OSAS and control group was found to be consistent with the literature (30, 31, 37).

In various studies, BMI was reported to be between 30-32 kg / m² in OSAS and 27-32kg / m² in the control group (30, 31). In our study, the mean BMI was 31,75±2,90 kg / m² in the patients and 25,82±2,33 kg / m² in the control group. BMI of OSAS patients was statistically significantly higher than control group. The present study concluded that BMI greater than 29,3 was identified as a risk factor for OSAS.

Uyar et al. found that the neck circumference was 45.50 ± 3.86 cm in the OSAS cases and 41.00 ± 3.94 cm in the control group (38). In our study, the mean neck circumference was 44,91±3,56 cm in the patient group and 39,03±2,81 cm in the control group. We also found that more than 42,1 cm of the neck circumference was identified as a risk factor for possible OSAS. Rubinstein et al. (39) in their study, rather than general obesity around the pharyngeal wall, excessive fat accumulation in the lateral pharyngeal fat pads are mentioned. Fleetham et al. (40) showed that there was a relationship

between the neck circumference and AHI due to the amount of fat accumulated in the neck area as a result of their MR examinations. The fact that our patient group had wider neck circumference compared to the control group was consistent with the literature findings.

Increased waist circumference is associated with the presence and severity of OSAS (41). In our study, waist circumference was significantly higher in OSAS patients. The mean waist circumference was $94,87 \pm 3,15$ cm in the patient group and $83,87 \pm 4,51$ cm in the control group. Waist circumference of more than 86.9 cm OSAS was determined as a predisposition factor in our study.

Limitations of the Study

The limitations of our study were the lack of OSAS duration, the inclusion of CPAP (Continuous Positive Airways Pressure) therapy and hypertension patients, lack of inflammation markers, unilateral measurement, no controlling of the potential effect of alcohol and the small number of patients.

CONCLUSION

In conclusion, early evaluation of OSAS patients is beneficial because it is an important and independent risk factor for cardiovascular and cerebrovascular diseases. Timely measurements of cIMT thickening which is accepted as precursor for these diseases, neck circumference and BMI may provide time for taking necessary measures for these diseases. The significant difference between the parameters of the neck regions between the two groups concluded that the mechanical and metabolic processes in the neck region were higher than the waist region. In addition, since NC has a linear relationship with cIMT, even only NC measurement can provide information about cIMT. This was the first study to determine an association between cIMT and NC in OSAS patient. To establish the relationship between cIMT and NC, a more comprehensive research should be undertaken in the future.

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