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A Strong Clue on Chest Radiography for Metabolic Syndrome in Patients with Obstructive Sleep Apnea: Aortic Arch Calcification

Obstrüktif Uyku Apneli Hastalarda Metabolik Sendrom İçin Göğüs Radyografisi Üzerinde Güçlü Bir İpucu: Aortik Ark Kalsifikasyonu

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ABSTRACT

Aim: Obstructive sleep apnea (OSA) is associated with increased atherosclerosis and metabolic syndrome (MetS). Vascular calcification plays a pivotal role in the development of atherosclerosis. However, data regarding vascular calcification and MetS is insufficient. The aim of the present study was to investigate the association between MetS and aortic arch calcification in patients with OSA.
Material and Methods: Patients who underwent an overnight polysomnography and diagnosed with OSA were enrolled into the study. Patients were classified into two groups based on the presence of MetS. Two examiners who were unaware of the results of polysomnographic assessment reviewed the chest radiograms.
Results: A total of 314 patients with OSA were included in the study. 33.1% of the patients were female and mean age was 51.2±10.9. Of these, 43.6% had mild OSA, 30.9% had moderate OSA, and 25.5% had severe OSA. Aortic arch calcification was detected in 56.4% (n=177) and MetS was detected in 58.6% (n=184) of the patients. Prevalence of aortic arch calcification was higher in patients with MetS than in those without MetS (p<0.001). By multiple logistic regression analysis found that body mass index (1.148, 95% CI, 1.089-1.210), apnea hypnea index (1.039, 95% CI, 1.016-1.062), and aortic arch calcification (4.986, 95% CI, 2.887-8.610) were found to be predictors of MetS.
Conclusion: Aortic arch calcification seen in chest radiography is strongly associated with MetS in patients with OSA. Aortic arch calcification may be an alerting finding for clinicians regarding the development of MetS in patients with OSA.
Keywords: Obstructive sleep apnea; aortic arch calcification; metabolic syndrome.

ÖZ

Amaç: Obstrüktif uyku apnesi (OSA), ateroskleroz ve metabolik sendrom (MetS) gelişimi için önemli bir risk faktörüdür. Vasküler kalsifikasyon ateroskleroz gelişiminde önemli bir rol oynamaktadır. Buna rağmen, literatürde MetS ile vasküler kalsifikasyon arasındaki ilişkiyi gösteren veriler yetersizdir. Bu çalışmanın amacı, OSA'lı hastalarda MetS ile aortik ark kalsifikasyonu arasındaki ilişkiyi araştırmaktır.
Gereç ve Yöntemler: Bir gece polisomnografi laboratuvarında yatan ve OSA tanısı koyulan hastalar çalışmaya dahil edildi. Hastalar MetS varlığına göre iki gruba ayrıldı. Polisomnografik değerlendirme sonuçlarından habersiz olan iki araştırmacı akciğer grafilerini inceledi.
Bulgular: Çalışmaya OSA tanısı alan toplam 314 hasta dahil edildi. Hastaların %33,1 kadın ve ortalama yaş 51,2±10,9 idi. Çalışmaya alınan hastaların %43,6'sında hafif OSA, %30,9'unda orta derecede OSA ve %25,5'inde ağır OSA varlığı saptandı. Hastaların %56,4'ünde (n=177) aortik ark kalsifikasyonu, %58,6'sında (n=184) ise MetS saptandı. Aortik ark kalsifikasyonu prevalansının MetS saptanan hastalarda MetS saptanamayan hastalara göre daha yüksek olduğu bulundu (p<0,001). Çoklu lojistik regresyon analizinde, vücut kitle indeksinin (1,148; %95 GA 1,089-1,210), apne hipopne indeksinin (1,039; %95 GA, 1,016-1,062) ve aortik ark kalsifikasyonunun (4,986; 95% GA 2,887-8,610) MetS varlığı için bağımsız prediktörler olduğu bulundu.
Sonuç: OSA'lı hastalarda akciğer grafisinde görülebilen aortik ark kalsifikasyonu ile MetS arasında güçlü bir ilişki olduğu bulundu. Aortik ark kalsifikasyonu, OSA'lı hastalarda MetS gelişimi ile ilgili klinisyenler için uyarıcı bir bulgu olabilir.
Anahtar kelimeler: Obstruktif uyku apne; aort ark kalsifikasyonu; metabolik sendrom.

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INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by intermittent partial or total obstruction of the upper airway during sleep (1). OSA is a systemic illness with debilitating effects on the cardiovascular system. Obesity is the most significant risk factor for the development of OSA, as is metabolic syndrome (MetS) which is usually accompanied by OSA (2). The increased prevalence of MetS causes a further increase in cardiovascular morbidity and mortality (3). MetS refers to the co-existence of metabolic disorders such as abdominal obesity, glucose intolerance or diabetes mellitus with insulin resistance, dyslipidemia, and hypertension. Each component of MetS is an independent risk factor for cardiovascular diseases (CVD). Moreover, the combination of these risk factors further increases the prevalence and severity of CVD (4). MetS starts with an increase in insulin resistance (5), which accelerates atherosclerosis and the development of type 2 diabetes. Inflammation, endothelial damage, reactive oxygen species, as well as vascular calcification play important roles in the pathogenesis of atherosclerosis (6).

Vascular calcification occurs due to calcium accumulation in the intima or the media layer of the vascular bed. Calcification of the vascular bed is an important predictor of subclinical atherosclerosis and cardiovascular events (7), and is associated with increased atherosclerotic plaques in the same vascular segment. Both OSA and MetS are risk factors for atherosclerosis, and synergistically accelerate its development (8). Therefore, we hypothesized that vascular calcification is increased in patients diagnosed with OSA and presenting symptoms of MetS. Aortic arch calcification (AAC) refers to the presence of calcified deposits in the aortic arch and a part of the descending aorta in standard chest x-rays (9). AAC is the easiest tool to assess vascular calcification and can be detected easily with a routine chest x-ray, a simple and cost-effective test. However, no data are available regarding the use of AAC in predicting MetS in patients with OSA. The aim of the present study, therefore, was to determine the association between AAC and Mets in patients with OSA.

MATERIAL AND METHODS

Clinical Characteristics of the Patients

Patients hospitalized at the sleep laboratory of Karabuk University between January 2015 and January 2017 were consecutively assessed. Inclusion criteria were as follows: a) age over 18 years, b) apnea/hypopnea index (AHI) ≥5, and c) willingness to participate in the study. Exclusion criteria were a) AHI <5, b) previous history of cardiac surgery, c) pregnancy, d) presence of active infection or malignancy, e) improper chest x-ray examination, or f) inconclusive sleep test. The patients were stratified into a non-MetS, or a MetS group based on the presence/absence of metabolic syndrome. A detailed medical history, including cardiovascular diseases/risk factors and current medications were obtained from all study participants. Hypertension was defined as blood pressure of ≥140/90 mm Hg and/or current use of antihypertensive medications. Patients who were on oral anti-diabetic agents and/or insulin treatment, or who had a fasting blood glucose level of ≥126 mg/dL, at least two times, were considered to have diabetes mellitus. Current smokers or patients who had quit smoking within the last month were regarded as smokers. Patients with total cholesterol level >200 mg/dL, low-density lipoprotein cholesterol (LDL-C) >100 mg/dL or receiving lipid-lowering medications were considered hyperlipidemic (10). The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (11). BMI was calculated by dividing the weight (kg) by the square of the height (m) (12), and BSA was calculated by dividing the square root of the weight (kg) and height (cm) by 3600 (13). Standard chest x-rays and echocardiograms were obtained from all patients. Abant Izzet Baysal University Clinical Researches Ethics Committee approved the study protocol (23.02.2017, 2015/19), and each subject gave written informed consent.

Definition of MetS

The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) defines MetS as follows; (i) waist circumference of >102 cm in males and >88 cm in females, (ii) fasting serum triglycerides ≥150 mg/dL or use of medical therapy for elevated triglycerides, (iii) HDL cholesterol <40 mg/dL in males and <50 mg/dL in females or use of medical therapy to reduce HDL cholesterol, (iv) high blood pressure, i.e., diastolic blood pressure ≥85 mmHg and systolic blood pressure ≥130 mmHg, or use of medical therapy for hypertension, or (v) high glucose levels (fasting serum glucose ≥100 mg/dL) or use of medical therapy for elevated glucose levels (4).

Evaluation of AAC

The standard chest x-ray (40 cm × 40 cm; Curix HT 1.000G Plus, Agfa, Mortsel, Belgium) was taken with the patient in standing position (Thoramat, Siemens, Erlangen, Germany), with a focus-patient distance of 150 cm. An automated exposure control with a fixed tube voltage of 117 kV was used. AAC was graded as follows: Grade 0 with no visible calcification, Grade I with small spots of calcification or thin calcification on the aortic knob, Grade II with one or more areas of thickened calcification, and Grade III with circular calcification on the aortic knob (9) (Figure 1). Two examiner who were blinded to the sleep laboratory findings reviewed AAC on the chest x-ray. One hundred chest x-rays randomly selected for AAC evaluation were independently evaluated by two cardiologists to assess the reliability of the AAC diagnosis, and the Kappa value was found to be 0.812 and $p<0.001$.

Polysomnography

The diagnosis of OSA was based on polysomnographic study (Alice Sleepware; Philips Respironics, Inc., Murrysville, Pa., USA). All variables were recorded on a commercially available computerized system, which included electroencephalography (F3M2, F4M1, C3M2, C4M1, O1M2 and O2M1), bilateral electrooculography, submental electromyography, uncalibrated inductive plethysmography which measured thoracic and abdominal movements, finger oximeter for measuring oxyhemoglobin saturation (SaO_2), thermistors to record airflow through the nose and mouth, two contiguous ECG leads, a snoring microphone and video monitoring with an infrared video camera. The entire recording was observed by an experienced sleep technician. Apnea was defined as the cessation of airflow for >10 sec, and hypopnea was defined as a reduction in airflow of ≥30% lasting for ≥10 sec accompanied by a decrease in oxygen saturation (SpO_2)

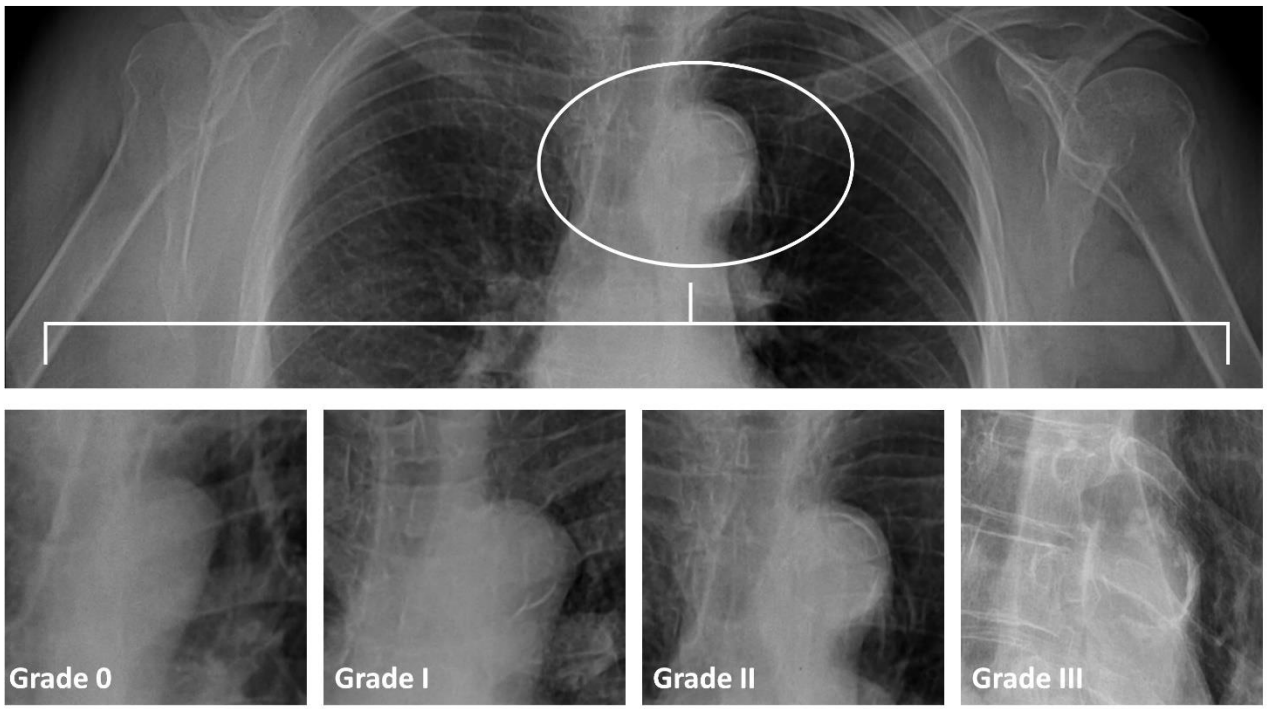


Figure 1. Grading of aortic arch calcification

by at least 3% (14). The duration for which SpO_2 was <90% during sleep and the minimum SaO_2 was calculated for each patient. Apnea-hypopnea index values were calculated as the number of episodes of apnea and hypopnea per hour over the total duration of sleep. Patients with an AHI ≥5 were considered to have OSA and enrolled in the study. The severity of OSA was classified according to the AHI (mild: ≥5 and <15, moderate: ≥15 and <30 and severe: ≥30) (15).

Echocardiographic Examination

All patients were examined using a commercially available system (Vivid 4; GE Medical Systems, Horten, Norway) with a phased-array 3.5-MHz transducer. The conventional M-mode, B-mode, and Doppler parameters were measured according to the American Society of Echocardiography guidelines. Left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters and posterior (PWT) and interventricular septal (IVST) wall thicknesses were measured. Left ventricular mass (LVM) was calculated using the Devereux equation: $LVM = 0.8 \times 1.04 \times [(LVEDD + IVST + PWT)^3 - (LVEDD)^3] + 0.6$; LVM index (LVMI) was calculated by dividing the LVM by the body surface area. Left ventricular hypertrophy was defined as LVMI >115 g/m^2 for men and >95 g/m^2 for women (16).

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) software was used for statistical analyses. All data were summarized using appropriate descriptive statistics (Mean, Standard Deviation, Median, Minimum, Maximum, Frequency and Percentage). Student's t test was used for comparison of variables with normal distribution while Mann-Whitney U test was used for comparison of variables with non-normal distribution. Backward multiple logistic regression analysis was used for the assessment of risk factors affecting MetS. Pearson's Chi-Square test was used for comparison of the qualitative data. The cutoff points based on MetS for statistically significant parameters were calculated by using Receiver operator characteristics (ROC) curve analysis. A p value of <0.05 were considered to be statistically significant.

RESULTS

Comparison of Clinico-Demographical Parameters

The study included 314 OSA patients, of which 105 (33.4%) were female, and the mean age of the cohort was 51.2±10.9 years. The mean BMI was 32.7±6.1 kg/m^2, mean waist circumference was 111.4±15.1 cm, and mean neck circumference was 40.4±4.1 cm. Eighty-three (26.4%) patients were smokers, 47.8% (n=150) had hypertension, 24.8% (n=78) had diabetes, and 7% (n=22) had hyperlipidemia (Table 1). AAC was detected in 56.4% (n=177) of the patients and 58.6% (n=184) had MetS (Table 2). In terms of sleep diagnosis, 43.6% (n=137) of the patients had mild OSA, 30.9% (n=97) had moderate OSA, and 25.5% (n=80) had severe OSA.

The MetS and non-MetS patient groups did not significantly differ in terms of age (p=0.193) or gender (p=0.909). In contrast, the BMI (p=0.001), waist circumference (p=0.001), and neck circumference (p=0.001) were significantly higher in the MetS group compared to the non-MetS group. The prevalence of hypertension (p=0.001), diabetes (p=0.014) and hyperlipidemia (p=0.022) were also significantly higher in the MetS group than in the non-MetS group. In addition, the systolic arterial (p=0.001) and diastolic arterial pressure (p=0.001) were significantly higher in the MetS group, as was left ventricular hypertrophy prevalence (p=0.015), LVESD (p=0.002), LA (p=0.002), IVST (p=0.003), PWT (p=0.001), and AHI (p=0.001) compared to the non-MetS group. In terms of biochemical indices, serum glucose (p=0.001), urea (p=0.048), triglycerides

(p=0.001), uric acid (p=0.004), CRP (p=0.046), and BSA (p=0.001) levels were significantly higher, while HDL (p=0.001), LVEF (p=0.001) and GFR (p=0.005) were significantly lower in the MetS patients compared to the non-MetS patients (Table 3). ROC curve analysis yielded a strong predictive ability of AAC for the presence of MetS (AUC=0.721, 95%CI 0.663 to 0.779, p<0.001). Presence of AAC on chest radiography had a sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 76.8%, 64.9%, 73.9%, 68.4% and 71.6%, respectively, for the presence of MetS (Figure 2).

Logistic Regression Analysis

The effects of different risk factors including BMI, neck circumference, AAC, LVH, LVEDD, LVESD, LA, AHI, SO_2 duration, CRP, BSA, LVEF, and GFR on MetS were assessed using backward logistic regression analysis. The model describing the risk factors is shown in Table 4. At the end of step 11, BMI, AAC, and AHI were the significant risk factors (p<0.001) affecting MetS. The explanatoriness coefficient of the model was 74.8%. The odds ratios were as follows; for BMI, 1.148 (95% CI, 1.089-1.210); for AAC, 4.986 (95% CI, 2.887-8.610); and for AHI, 1.039 (95% CI, 1.016-1.062).

DISCUSSION

The prevalence of MetS is higher in patients with OSA (17), and is also the reason for the higher cardiovascular risk seen in these patients. Consistent with previous studies (17), the prevalence of MetS in patients with OSA was 58.6% in the present study. In addition, we found an independent and strong association between MetS and AAC in patients with OSA. Vascular calcification increases with age and has debilitating effects on the cardiovascular system. It results in increased arterial stiffness and myocardial workload, and impaired diastolic coronary perfusion, resulting in a higher risk of stroke, hypertension, myocardial infarction, diabetes mellitus, renal failure, hyperlipidemia, and left ventricle hypertrophy (18-21). Consistent with previous studies, we found that AAC increased with age and was significantly associated with hypertension, diabetes, hyperlipidemia and left ventricular hypertrophy, in addition to being negatively correlated with GFR.

The important factors affecting vascular calcification in patients with OSA and MetS include intermittent hypoxia, inflammation, oxidative stress, and the renin-angiotensin system (22-24). Several studies have shown an association between OSA and vascular calcification (25,26) and consistent with these studies, we also found an association between AHI and AAC, a prototype for vascular calcification, suggesting that the latter could also be the cause of increased arterial stiffness in patients with OSA. In fact, vascular calcification has been shown to play the main role in increased arterial stiffness (27). Arterial stiffness increases due to the presence and severity of OSA irrespective of hypertension and obesity (1). We demonstrated a strong association between OSA and AAC, which suggests that increased arterial stiffness in OSA patients may be due to increased vascular calcification. In addition, we found an independent and strong association between MetS and AAC, suggesting that the increased prevalence of vascular calcification in OSA patients may be due to increased prevalence of MetS.

Table 1. Baseline characteristics of groups

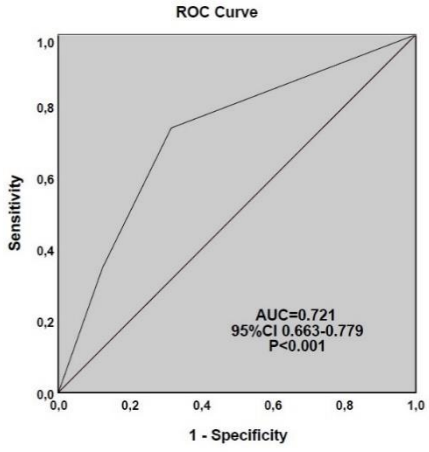
	Non-MetS (n=130)	MetS (n=184)	p
Age (year)	50.2±10.9	51.9±10.9	0.193
Female gender, n (%)	43 (33.1)	62 (33.7)	0.909
Body mass index (kg/m2)	30.2±5.8	34.6±5.6	**0.001**
Waist circumference (cm)	104.7±14.9	116.1±13.3	**0.001**
Neck circumference (cm)	39.2±4.2	41.2±3.8	**0.001**
Smoking, n (%)	35 (26.9)	48 (26.1)	0.869
Hypertension, n (%)	47 (36.2)	103 (56.0)	**0.001**
Diabetes mellitus, n (%)	23 (17.7)	55 (29.9)	**0.014**
Hyperlipidemia, n (%)	4 (3.1)	18 (9.8)	**0.022**
Systolic blood pressure (mm Hg)	119.7±13.9	127.6±15.7	**0.001**
Diastolic blood pressure (mm Hg)	72.6±10.0	76.9±10.4	**0.001**
Apnea Hypopnea Index (events/h)	11 (5-50)	20 (5-88)	**0.001**
Lowest SO_2 (%)	80 (0-97)	78 (0-93)	0.318
Time SO_2 <90 (min)	15 (0-96)	21 (0-96)	0.078
Total sleep time (min)	376.0±53.2	376.8±55.7	0.894
Obstructive sleep apnea, n (%)			
Mild	77 (59.2)	60 (32.6)	
Moderate	36 (27.7)	61 (33.2)	**0.001**
Severe	17 (13.1)	63 (34.2)	

MetS: metabolic syndrome, continuous variables distributed normally summarized with mean±standard deviation while median (minimum-maximum) were used for variables distributed not normally

Table 2. Aortic arch calcification grades in groups, n (%)

	Non-MetS (n=130)	MetS (n=184)	p
Aortic arch calcification			
Grade 0	89 (68.5)	48 (26.1)	
Grade 1	25 (19.2)	72 (39.1)	**<0.001**
Grade 2	12 (9.2)	48 (26.1)	
Grade 3	4 (3.1)	16 (8.7)	
Grade ≥1	41 (31.5)	136 (73.9)	**<0.001**
Grade ≥2	16 (12.3)	64 (34.8)	**<0.001**
Grade ≥3	4 (3.1)	16 (8.7)	**0.045**

MetS: metabolic syndrome



AUC: Area under the curve, AAC: Aortic arch calcification, CI: Confidence interval

Figure 2. ROC curve analysis for AAC

Table 3. Laboratory and echocardiographic findings

	Non-MetS (n=130)	MetS (n=184)	p
Left ventricular end-diastolic diameter (mm)	47.3±4.1	48.3±4.5	0.059
Left ventricular end-systolic diameter (mm)	29.1±4.6	30.8±4.8	**0.002**
Left atrial diameter (mm)	35.8±3.1	36.9±2.9	**0.002**
Interventricular septal thickness (mm)	11.2±1.3	11.6±1.4	**0.003**
Posterior wall thickness (mm)	10.4±0.9	10.8±1.0	**0.001**
E (cm/sec)	40-127 (70)	43-135 (70)	0.808
A (cm/sec)	32-115 (75)	38-136 (76)	0.619
E/A	0.6-1.9 (0.9)	0.5-2.2 (0.9)	0.693
Glucose (mg/dL)	65-283 (95.5)	58-422 (104)	**0.001**
Urea (mg/dl)	12.7-96 (29.2)	13-80 (32)	**0.048**
Creatinine (mg/dL)	0.8±0.2	0.9±0.2	0.054
Total cholesterol (mg/dL)	193.5±38.7	199.8±40.2	0.169
Triglyceride (mg/dL)	40-447 (129.5)	63-511 (188)	**0.001**
High-density lipoprotein (mg/dL)	42.9±7.7	38.6±7.7	**0.001**
Low-density lipoprotein (mg/dL)	120.1±33.5	117.7±34.2	0.528
Gama-glutamyl transferase, (U/L)	7-160 (25)	7-395 (25)	0.831
Uric acid, (mg/dL)	5.6±1.6	6.1±1.6	**0.004**
C-reactive protein, (mg/L)	0-22.7 (2.7)	0-21 (3.5)	**0.046**
Body surface area (m^2)	2.0±0.2	2.1±0.2	**0.001**
Left ventricular mass index (gr/m^2)	92.7±20.2	95.2±20.1	0.289
Left ventricular ejection fraction (%)	63.2±7.2	60.2±8.0	**0.001**
Glomerular filtration rate ($mL/min/1.73m^2$)	99.0±11.4	95.5±10.9	**0.005**

MetS: metabolic syndrome, continuous variables distributed normally summarized with mean±standard deviation while median (minimum-maximum) were used for variables distributed not normally

Table 4. Logistic regression analysis for metabolic syndrome

	OR	95% CI	p
Body mass index	1.148	1.089 - 1.210	**0.001**
Aortic arch calcification ≥1	4.986	2.887 - 8.610	**0.001**
Apnea Hypopnea Index	1.039	1.016 - 1.062	**0.001**

OR: Odds ratio, CI: Confidence Interval

MetS is frequently seen in patients with OSA. Parish et al. (17) reported a 60% prevalence of MetS in patients with OSA; in accordance with this, we found it to be 58.6% in the present study. Insulin resistance forms the basis of MetS and is known to accelerate vascular calcification (5). In addition, the individual components of MetS including hypertension, diabetes, hyperlipidemia, and obesity have also been associated with vascular calcification (28,29). Therefore, it is highly likely that the deleterious effect of vascular calcification on the cardiovascular system is a result of the synergistic action of the illnesses constituting MetS. An association has been demonstrated between MetS and calcification in the mammary gland (30), coronary arteries (31), and thoracic arteries (32). In addition to further strengthening the known association between vascular calcification and MetS, the results of the present study are also the first to show an association between MetS and vascular calcification in patients with OSA.

Another important finding of the present study is that BMI and apnea/hypopnea index were found to be other independent predictors of MetS. Based on these results, we hypothesize that in addition to obesity, OSA is an important risk factor for MetS. Consistent with our results, Alam et al. have reported obesity as one of the most important risk factors for both OSA and MetS, acting via induction of inflammatory pathways (33). Further, the close link between MetS and apnea/hypopnea index shows that the prevalence of MetS increases with the severity of OSA. Consistent with our results, Parish et al. (17) have shown a close relationship between MetS and AHI.

CONCLUSION

Obstructive sleep apnea is frequently accompanied by metabolic syndrome. Detection of MetS is an essential part of treatment. AAC seen in chest radiography is strongly associated with MetS in patients with OSA. AAC may be an alerting finding for clinicians regarding the development of MetS in patients with OSA.

Limitations

This study has several limitations. First, it was a single-center study and had a relatively low number of patients. Second, only OSA patients were included. Thus, our results cannot be generalized for all cases. Third, we did not study possible mechanistic link between MetS and AAC. Fourth, AAC grading was performed with visual observation of chest x-ray which may reduce its

reproducibility. Finally, we did not study prognostic significance of the AAC for MetS in patients with OSA.

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Disclosure of Interest
The authors report no conflicts of interest exist.

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