Relationship Between Obstructive Sleep Apnea and Increased Thoracic Periaortic Adipose Tissue

Obstrüktif Uyku Apnesi ve Artmış Göğüs Periaortik Yağ Dokusu Arasındaki İlişki

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ABSTRACT Objective: Aim of this study is to demonstrate the increased thoracic periaortic adipose tissue volume which is related to increased cardiovascular risk in subjects with obstructive sleep apnea (OSA) compared to control group. **Material and Methods:** The study population consisted of 25 newly diagnosed OSA patients (mean (SD) age: 55.0 (±12.1) years, 64% were males) and 34 healthy volunteers (mean (SD) age: 53.2 (±11.8) years, 61.8% were males). Standard overnight polysomnography system had applied to all of the participant and apnea–hypopnea index (AHI) was calculated. In addition, all of the participants underwent thoracic radiographic assessment in the supine position, using an 8-slice multidetector computed tomography scanner and thoracic periaortic adipose tissue volume was measured. Control group and OSA group were compared according to demographic characteristics, anthropometrics measurements and laboratory findings. **Results:** In subjects with OSA, thoracic periaortic adipose tissue volume [50.3 (±14.9) cm^3 vs. 19.6 (±8.4) cm^3, p<0.001], apnea-hypopnea index (AHI) [19.9 (±9.5) vs. 2.7 (±1.1) p<0.001)], triglyceride [204.7 (±87.1) mg/dL vs. 145.1 (±40.2) mg/dL (p= 0.003)] and total cholesterol [204.7 (±39.6) mg/dL vs. 183.5 (±36.1) (p=0.041)] levels were significantly higher compared to the control group. While there was a positive correlation between thoracic periaortic adipose tissue and AHI, no correlation was found with the other parameters. In stepwise regression analysis, AHI emerged as a significant predictor of thoracic periaortic adipose tissue (r= 0.41, p= 0.038), contributing to 13.7% of its variability. In OSA subjects, no significant difference was noted in thoracic periaortic adipose tissue levels with respect to gender (p=0.72), total cholesterol (p= 0.53), triglyceride (p= 0.34), or smoking status (p=0, 32). **Conclusion:** Our findings indicate significantly higher values for thoracic periaortic adipose tissue in OSA than controls, being associated positively with dyslipidemia and strongly predicted by AHI levels in OSA subjects, while not differing with respect to gender, and smoking status.

Key Words: Sleep apnea, obstructive; dyslipidemias

ÖZET Amaç: Bu çalışmanın amacı kontrol grubuna göre obstrüktif uyku apne (OSA) hastalarında kardiyovasküler risk faktörleri ile ilgili olan torasik periaortik yağ dokusu (TAT) düzeyinin arttığını göstermektir. **Gereç ve Yöntemler:** Çalışma populasyonu 28 yeni tanı OSA hastasından (ortalama (SD) yaş: 55,0 (±12,1) yıl, %64 erkek) ve 37 sağlıklı gönüllüden (ortalama (SD) yaş: 53,2 (±11,8) yıl, %61,8 erkek) oluşmaktadır. Tüm katılımcılara standart polisomnografi sistem uygulandı ve apne–hipopne indeksi (AHI) hesaplandı. Ayrıca tüm katılımcılara supin pozisyonda torasik radyografi uygulanarak 8 kesitli multidedektör bilgisayarlı tomografi ile TAT hacmi ölçüldü. Kontrol grubu ve OSA grubu demografik karakterleri, antropometrik ve laboratuar bulguları yönünden karşılaştırıldı. **Bulgular:** OSA grubundaki hastalarda, TAT volüm [50.3 (±14,9) cm^3 vs. 19,6 (±8,4) cm^3, p<0.001], (AHI) [19,9 (±9,5) vs. 2,7 (±1,1) p<0,001)], trigliserid 204.7 (±87,1) mg/dL vs. 145,1(±40,2) mg/dL (p=0,003)] ve total kolesterol [204,7 (±39,6) mg/dL vs. 183,5 (±36,1) (p=0,041)] düzeyleri kontrol grubuna göre anlamlı derecede yüksek bulundu. TAT ile AHI (r=0,441; p=0,027) arasında pozitif korelasyon varken diğer parametrelerle korelasyon saptanamadı. Aşamalı regresyon analizinde AHI TAT için önemli bir belirteç olarak ortaya çıktı (β= 0,414, p= 0,038). OSA hastalarında TAT düzeyi cinsiyet (p=0,728) ya da sigara içiciliği durumu (p=320) açısından farklılık göstermedi. **Sonuç:** Bizim bulgularımız incelendiğinde OSA hastalarında TAT volümü kontrol grubuna göre önemli derecede yüksekti ve dislipidemi ile pozitif korelasyonu vardı. OSA hastalarında TAT için AHI düzeyi güçlü bir belirleyici iken cinsiyet ve sigara içiciliği yönünden fark göstermedi.

Anahtar Kelimeler: Uyku apnesi, tıkayıcı; dislipidemiler

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Obstructive sleep apnea (OSA) is characterized by episodes of the cessation of the breathing during sleep, fragmentation of sleep period, oxygen desaturation and somnolence during daytime.[1] Men are more frequently affected and it is seen in the 1-5% of the population.[2] Combined effects of hypoxemia during apneic episodes, systemic hypertension and increased sympathetic activity are accused for the development of atherosclerosis.[3] Previous studies have demonstrated that cardiovascular system related complications such as systemic arterial hypertension, coronary artery disease (CAD), congestive heart failure, cardiac arrhythmia, and pulmonary hypertension are increased in subjects with OSA.[3]

OSA is frequently associated with obesity. Most patients with OSA have central obesity and increased visceral fat.[4] The important matter in OSA are sleep fragmentation. Sleep fragmentation can cause to sleep deprivation, reduced physical activity, daytime somnolence, and finally weight gain.

Relation between visceral adipose tissue (including visceral abdominal, pericardial, and thoracic periaortic adipose tissue) and metabolic risk factors and also metabolic syndrome are more pronounced compared to subcutaneous fat tissue.[5] Increase in the visceral fat tissue results in the increase in basal and catecholamine induced lipolysis response. Dedicated the evidence that adipose sections disturb in their endocrine efficiency reduce susceptibility to insulin induced antilipolysis, thereby the relationship morbidity and metabolic risk.[6] Visseral fat hypertrophy is related to increased inflammatory activity.[7,8] Pericardial fat and visseral adipose tissue (VAT) were demonstrated to display differences in adiponectin, leptin, and interleukin-6 secretions.[9]

Epicardial adipose tissue (EAT), which is a subtype of VAT, may play a key role in the pathogenesis and development of CAD. Mariani et al. had demonstrated that EAT was an independent marker for cardiovascular disease (CVD) in subjects with OSA.[10] Thoracic periaortic adipose tissue is a subtype of perivascular fat that can be quantified using multidetector computed tomography (MDCT).[11] Thoracic periaortic adipose tissue could be considered a novel risk marker for CVD.[12] Studies have shown that compared to other adiposity measures, thoracic periaortic adipose tissue was shown to be more strongly associated with cardiometabolic risk profiles and subclinical atherosclerosis in an otherwise relatively healthy population.[6]

Despite the relation between thoracic periaortic adipose tissue and CVD and CAD had demonstrated in several studies, there is no literature about the thoracic periaortic adipose tissue levels in OSA subjects. Thoracic periaortic adipose tissue may certainly associate with both apnea-hipopnea index and recommend that this undiscovered factor might have the feature to highlight in individuals the risk to bring out OSA and cardiovascular diseases. Thoracic periaortic adipose tissue may be also considerable and independently associated to other conventional cardiovascular risk determinants. Considering the 26% risk of OSA in adult population, aim of this study is to evaluate the cardiovascular risk by comparing the thoracic periaortic adipose tissue volume measured by MDCT in OSA subjects and control group.[7]

MATERIAL AND METHODS

PATIENT SELECTION

A study population consisted of 25 diagnosed OSA subjects [mean (SD) age: 55.0 (±12.1) years, 64% were males] and 34 healthy volunteers who had evaluated for the presence of OSA but did not have the diagnosis [mean (SD) age: 53.2 (±11.8) years, 61. 8% were males]. The healthy volunteers had the same clinical variables as the patient group, who were referred to the Mevlana University Department of Chest Disease between January 2014 and January 2015. All subjects underwent overnight polysomnography was recorded with Alice® 6 Polysomnography System (ALICE 6 L De model,31 canal PSG system, USA) which recorded the following parameters: electrocardiogram, central, temporal and occipital electroencephalogram, bilateral electrooculograms, submental and anterior tibialis electromyogram, nasal airflow using a nasal

cannula and pressure transducer, nasal-oral airflow using thermistor and respiratory effort using chest and abdominal piezo electric belts. The electromyelogram, electrooculogram and electroencephalogram leads were applied according to the international 10/20 electrode placement system. Oxyhemoglobin saturation was monitored using a pulse oximeter. Sleep stages were scored according to the criteria of American Academia of Sleep Medicine. Apnea were defined as decrements in airflow ≥ 90 % from baseline for ≥ 10 s. Hypopneas were defined as a 30 % or greater decrease in flow lasting at least 10 s and associated with a 4% or greater oxyhemoglobin desaturation. The number of apneas and hypopneas per hour of sleep was calculated to obtain the apnea-hypopnea index (AHI). The mean and minimal arterial oxyhemoglobin saturations and cumulative time spent with an arterial oxyhemoglobin saturation <90% were also calculated. Subjects were also excluded if they had CAD, percutaneous or surgical revascularization, peripheral artery disease, atrial fibrillation, active chronic obstructive lung disease, heart failure, chronic kidney disease, hypertension (HT), diabetes mellitus (DM), pericarditis, congenital heart disease, hepatic disease, diagnosis of upper airway resistance syndrome, diagnosis of psychiatric disease, using drugs for the psychiatric disease, hyperthyroidism, alcohol abuse problems or body mass index (BMIs) indicating morbid obesity (BMI ≥40 kg/m^2). The control group consisted of healthy individuals without chronic kidney disease, CAD, vasculitic lesions, DM, hepatic parenchymal disease or acute infection. The study was approved by the ethics board and written informed consent was obtained from all study participants.

Weight and height were measured in light clothing without shoes. BMI was calculated by dividing the weight by the height squared (kg/m^2). Blood pressure measurements were obtained from each patient in the seated position, using a standard mercury sphygmomanometer on the right arm. Following a 12-h nighttime fast, venous blood samples were obtained from the antecubital vein to measure serum fasting blood glucose (FBG; mg/dL), total cholesterol (mg/dL), high density lipoprotein cholesterol (HDL-C; mg/dL), low density lipoprotein-cholesterol (LDL-C; mg/dL), triglyceride (TG; mg/dL), aspartate aminotransferase (AST; mg/dL), alanine aminotransferase (ALT; mg/dL), blood urea nitrogen (BUN; mg/dL) and creatinine (mg/dL) in both patient and control groups. Levels of total cholesterol, HDL-C and TG were determined with enzymatic colorimetric assays using spectrophotometry. LDL-C was calculated using the Friedewald formula.

Comparisons between patient and control groups used demographic characteristics, anthropometrics and laboratory findings. Thoracic periaortic adipose tissue volume was evaluated in relation to demographic and clinical characteristics of OSA subjects and compared with other clinical parameters.

MDCT PROTOCOL AND MEASUREMENT OF THORACIC PERIAORTIC ADIPOSE TISSUE VOLUME

All participants underwent thoracic radiographic assessment in the supine position using an 8-slice MDCT scanner (Somatom Sensation 64, Siemens, Forchheim, Germany). All image analyses were performed on a dedicated workstation (Volume Analysis Software, Siemens, Leonardo), while adipose tissue quantification was performed using a semi-automated method that required manually defining ROI (region of interest) borders. Computed tomography (CT) attenuation thresholds were used to identify fax pixels (window width -200 to -450 HU) to calculate adipose volumes (cm^3). Thoracic periaortic adipose tissue was defined as the area immediately surrounding the thoracic aorta anteriorly by a horizontal line through the esophagus, connected to the left costo-vertebral joint, posteriorly by the anterior edge of the vertebral body, and the right lateral border of the vertebral body.[14] Thoracic periaortic adipose tissue was evaluated using a CT protocol by an experienced radiologist, who was blinded from patient baseline characteristics (Figure 1a, 1b).

CARDIOVASCULAR RISK FACTORS

Cardiovascular disease and metabolic risk factors were measured using standardized definitions. BMI

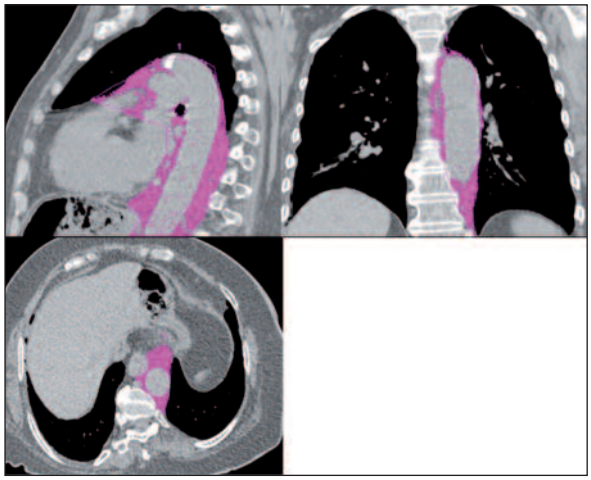

FIGURE 1a: Patients group; image of thoracic periaortic adipose tissue volume on MDCT.
(See color figure at
http://www.turkiyeklinikleri.com/journal/ic-hastaliklari-dergisi/500/tr-index.html)

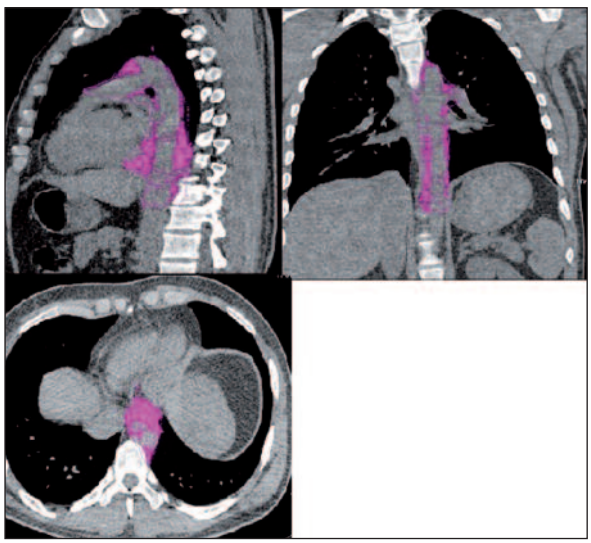

FIGURE 1b: Control group; image of thoracic periaortic adipose tissue volume on MDCT.
(See color figure at
http://www.turkiyeklinikleri.com/journal/ic-hastaliklari-dergisi/500/tr-index.html)

was calculated as weight in kilograms divided by the square of the height in meters. To measure blood lipids and glucose, fasting morning samples were collected. Smoking was defined as smoking at least one cigarette per day in the year prior to the physical exam. Hypertension was defined as using an anti-hypertensive medication or displaying a systolic blood pressure ≥140 mmHg, or a diastolic blood pressure ≥90 mmHg.

STATISTICAL ANALYSIS

Statistical analysis was carried out using the software Statistical Package for Social Sciences (SPSS; version 16.0, SPSS Inc. Chicago, IL, USA). The Kolmogorov–Smirnov test was applied to check normality of variables. The Chi-square (χ^2) test was used for the comparison of categorical data, and the Student's *t*-test was used for the comparison of parametric variables. Statistical correlation was assessed using Pearson's test. Data were expressed as mean (±standard deviation; SD) and percentage (%) accordingly. A value of $p<0.05$ was considered statistically significant.

RESULTS

DEMOGRAPHIC CHARACTERISTICS AND CLINICAL FINDINGS IN THE STUDY GROUPS

There was no difference with regard to age, sex, anthropometric measurements, and smoking status between OSA subjects and control group. In subjects with OSA, thoracic periaortic adipose tissue volume [50.3 (±14.9) cm^3 vs. 19.6(±8.4) cm^3, $p<0.001$], apnea–hypopnea index (AHI) [19.9 (±9.5) vs. 2.7 (±1.1) $p<0.001$)], triglyceride [204.7 (±87.1) mg/dl vs. 145.1(±40.2) mg/dl ($p=0.003$)] and total cholesterol [204.7 (±39.6) mg/dl vs. 183.5 (±36.1) ($p=0.041$)] levels were significantly higher compared to the control group (Table 1).

THORACIC PERIAORTIC ADIPOSE TISSUE VOLUME IN SUBJECTS WITH RESPECT TO DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

In OSA subjects, no significant difference was noted in thoracic periaortic adipose tissue levels with respect to gender ($p=0.72$) or smoking status ($p=0, 32$) (Table 2).

CORRELATION OF THORACIC PERIAORTIC ADIPOSE TISSUE VOLUME WITH OTHER CLINICAL PARAMETERS

There was a strong correlation between thoracic periaortic adipose tissue and AHI ($r=0.441$; $p=0.027$); however, there was no significant relationship found with other parameters (Table 3).

TABLE 1: Demographic and clinical characteristics in patient and control groups.

	Obstructive Sleep Apnea (n=25)	Control (n=34)	
	Mean (±SD)		p
Age (year)	55.0 (±12.1)	53.2 (±11.8)	0.58
Gender	n (%)		
Male	16 (64)	21 (61.8)	0.42
Female	9 (36)	13 (38.2)	
Smoking (present)	12 (48)	13 (38.2)	0.31
	Mean (±SD)		
Body mass index (kg/m^2)	27.1 (±3.7)	27.3 (±3.9)	0.90
Thoracic periaortic adipose tissue (cm^3)	50.3 (±14.9)	19.6 (±8.4)	<0.001
Apnea–hypopnea index	19.9(±9.5)	2.7 (±1.1)	<0.001
Fasting blood glucose (mg/dL)	93.1 (±7.8)	90.7 (±7.1)	0.24
Blood urea nitrogen (mg/dL)	24.1 (±7.2)	29.6 (±6.6)	0.24
Creatinine (mg/dL)	0.8 (±0.2)	0.7 (±0.2)	0.48
Aspartate aminotransferase (mg/dL)	29.7 (±7.1)	27.0 (±7.3)	0.18
Alanine aminotransferase (mg/dL)	30.6 (±6.8)	28.7 (±9.4)	0.37
Total cholesterol (mg/dL)	204.7 (±39.6)	183.5 (±36.1)	0.041
Triglyceride (mg/dL)	204.7 (±87.1)	145.1(±40.2)	0.003
High density lipoprotein-cholesterol (mg/dL)	43.0 (±14.1)	41.6 (±9.9)	0.66
Low density lipoprotein-cholesterol (mg/dL)	115.6 (±40.9)	106.5 (±20.1)	0.31
Hemoglobin (g/dL)	13.4 (±1.5)	13.1 (±1.4)	0.30

TABLE 2: Thoracic periaortic fat volume with respect to demographic and clinical characteristics among patients with obstructive sleep apnea and control patients.

Obstructive Sleep Apnea (n=25)	Thoracic periaortic adipose tissue volume Mean (±SD)	p-value	Control (n=34)	Thoracic periaortic adipose tissue volume Mean (±SD)	p-value
Gender					
Female (n=9)	51.4 (17.1)	0.72	Female (n=13)	20.9 (8.3)	0.64
Male (n=16)	49.3 (13.4)		Male (n=21)	18.8 (5.6)	
Smoking					
Yes (n=12)	53.5 (15.6)	0.32	Yes (n=13)	20.5 (7.9)	0.58
No (n=13)	47.4 (14.3)		No (n=21)	19.2 (6.4)	

LINEAR REGRESSION ANALYSIS FOR CORRELATES OF THORACIC PERIAORTIC ADIPOSE TISSUE

In stepwise regression analysis, AHI emerged as a significant predictor of thoracic periaortic adipose tissue (r= 0.41, p= 0.038), contributing to 13.7% of its standart error estimate No significant difference was noted in thoracic periaortic adipose tissue levels with respect to total cholesterol (p=0.53), triglyceride (p=0.34).

DISCUSSION

Aim of this study was to evaluate the relation between thoracic periaortic adipose tissue volume and cardiovascular risk in OSA subjects, and the results have demonstrated that thoracic periaortic adipose tissue volume was significantly higher in OSA subjects compared to control group and there was a positive correlation with AHI levels. Tho-

TABLE 3: Correlation of thoracic periaortic adipose tissue volume with other clinical parameters.

	r	p
Age (year)	-0.15	0.47
Body mass index (kg/m^2)	0.26	0.19
Fasting blood glucose (mg/dL)	0.24	0.23
Apnea–hypopnea index	0.44	0.027
Total cholesterol (mg/dL)	0.13	0.53
Triglyceride (mg/dL)	0.19	0.34
Low density lipoprotein-cholesterol (mg/dL)	0.33	0.10
High density lipoprotein-cholesterol (mg/dL)	0.34	0.08
Aspartate aminotransferase (mg/dL)	0.21	0.31
Alanine aminotransferase (mg/dL)	0.28	0.16

racic periaortic adipose tissue volume a well-established body fat depot with substantial impact for OSA. Thoracic periaortic adipose tissue were considerable increased in apneic individuals and the prevalence of thoracic periaortic adipose tissue was remarkable higher in the OSA group. Strongly predicted by AHI levels, while not differing with respect to gender and smoking status in OSA subjects. The significance of our study is that thoracic periaortic adipose tissue volume was detected for the the first time in subjects with OSA.

There are proofs about the causal relationship between cardiovascular morbidity and mortality and OSA.[8-11] Recent studies have demonstrated that even in the absence of classical risk factors, atherosclerotic cardiovascular changes develops at early ages in OSA subjects.[12] One longitudinal study had also reported that in subjects who had no cardiovascular disease and DM at the beginning of the study, at end of 7 years of follow up OSA was found to be an important risk factor for the development of cardiovascular diseases.[13] It was also demonstrated that 50% of the subjects who had significant OSA had cardiovascular disease.[14]

A great deal of experimental researchs sustain a probable link between VAT and biological pathways considerable in the pathogenesis of various disease results. For instance; visceral adiposity was related with case CVD and cancer above and beyond waist circumference or BMI.[15,16] Adipokines, biologically dominant molecules secreted from adipose tissue, are important key factors of these pathways and contain inflammatory activity. Adipokines are secreted from visceral adiposity and shows increased inflammatory activity and after correction with clinical risk factors and excessive lipoidosis is related to CVD.[17,18]

There are strong evidences that supports that VAT as a result of showing various endocrine activities increases metabolic risk and morbidity.[19] Perivascular fat is one such visceral fat storethat has been postulated to have a local pathogenic effect on blood vessels.[20,21] Thoracic periaortic adipose tissue is a subtype of perivascular fat[11] and because thoracic periaortic adipose tissue can be directly wrapped around the aorta, this distinct anatomic location could explain the specific correlation between high thoracic periaortic adipose tissue and high CVD among OSA individuals. Nonetheless, compared to other adiposity measures, thoracic periaortic adipose tissue was shown to be more strongly associated with cardio metabolic risk profiles and subclinical atherosclerosis in an otherwise relatively healthy population.[22]

In past studies conducted with participants from the Framingham Heart Study, a high volume of thoracic periaortic adipose tissue was reported to be associated with adverse cardiometabolic features among the subset of individuals with normal VAT, despite similar prevalence of various fat depots.[11] In our previous study we have demonstrated that thoracic periaortic adipose tissue volume was 40.1 cm^3 in subjects with type 2 DM, and there was a positive correlation between thoracic periaortic adipose tissue volume and BMI, serum levels for FBG, HbA1c, total cholesterol, and LDL serum levels.[23] In our present study, thoracic periaortic adipose tissue volume was 19.6 (±8.4) cm^3 in the control group and 50.3 (±14.9) cm^3 in the OSA group, and the difference was found to be statistically significant ($p<0.001$). The increased inflammatory state and sympathetic activity due to intermittent hypoxia and sleep fragmentation could perform a role in the modulation of paracrine effectiveness of thoracic periaortic adipose tissue volume. We uncovered a strong positive correlation between thoracic periaortic adipose tissue vol-

ume and AHI levels. This is related to increased CVD risk in OSA subjects and shows that risk is increasing with AHI levels. Results of our study have shown that even at lower AHI levels, CVD risk is increased in OSA subjects.

In addition previous studies have also demonstrated that obesity increases the prevalence of OSA, especially subjects who had BMI > 29 had 8-12 times increased risk for OSA and among obese subjects 50-77% had OSA.[16] Studies have shown that thoracic periaortic adipose tissue is associated with BMI, which is a definite metabolic risk factor.[11,12,24] But in the present study, there was no association between thoracic periaortic adipose tissue and BMI. So it may be concluded that thoracic periaortic adipose tissue is an independent predictor of atherosclerosis and CVD.

However, it is well known that BMI is not a good measure of body adiposity and different factors beyond BMI are associated with OSA, with abdominal fat, gender and age being significant predictors of sleep disordered breathing.[17] Sex-associated variations in the amount of visceral fat storage could make a contribution to the severe prevalence of OSA in men.[18] In recent years a number of researchs have recommended a serious bidirectional relationship between CVD and OSA.[18] Remarkably, the amount of adipose tissue near to the pharyngeal airway and in the intraperitoneal space associates with AHI, but not with BMI.[19] These informations consolidate the assumption that BMI is not a beneficial estimation factor of OSA, whether abdominal fat indices is better susceptible factor for estimation.[25-27]

In conclusion, our findings indicate significantly higher values for thoracic periaortic adipose tissue in OSA than controls, being associated positively with AHI levels and strongly predicted by AHI levels in OSA subjects, while not differing with respect to gender and smoking status.

STUDY LIMITATIONS

The subjects included in the study were a small group of individuals visiting the internal medicine and chest disease outpatient clinic, which makes it difficult to extend the present findings to the general population. The study's sample size and number of thoracic periaortic adipose tissue volumes are adequate to provide sufficient statistical power. Our findings need to be confirmed and validated in much larger studies using appropriate reclassification statistics to provide value to existing risk scores.

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