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Association Between Serum Fetuin-A levels, Carotid Artery Stiffness, and Intima–Media Thickness in Patients With Normotensive Obstructive Sleep Apnea Syndrome

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Abstract

Increased carotid intima–media thickness (cIMT) and stiffness, reflecting subclinical atherosclerosis, are associated with obstructive sleep apnea syndrome (OSAS). The relationship between serum fetuin-A, which inhibits ectopic calcification, and atherosclerosis is unclear. Therefore, we investigated the association between serum fetuin-A levels and carotid artery stiffness and cIMT in patients with normotensive OSAS (n = 50) and non-OSAS controls (n = 38). Compared with controls, there were lower fetuin-A levels (59.4 $\pm$ 6.5 vs 68.2 $\pm$ 5.8 ng/mL, $P = .029$), higher mean cIMT (0.73 $\pm$ 0.2 vs 0.63 $\pm$ 0.3 mm, $P < .001$), and greater stiffness (β) index (7.45 $\pm$ 0.9 vs 5.2 $\pm$ 0.7, $P = .001$) in the OSAS group. The cIMT and stiffness (β) index were inversely correlated with fetuin-A levels ($r = -.324$, $P = .033$; $r = -.466$, $P < .001$, respectively) and positively correlated with apnea hypopnea index ($r = .498$, $P < .001$; $r = .422$, $P = .001$, respectively) in the OSAS group. Decreased serum fetuin-A levels were associated with subclinical carotid atherosclerosis in patients with normotensive OSAS.

Keywords

carotid atherosclerosis, fetuin-A, obstructive sleep apnea, intima–media thickness

Introduction

Many studies have investigated the relationship between obstructive sleep apnea syndrome (OSAS) and cardiovascular disease (CVD) such as cardiac arrhythmias, coronary artery disease (CAD), systolic heart failure, hypertension, and stroke.[1-7] The proposed potential mechanisms of CVD in OSAS are increased oxidative stress, endothelial dysfunction, low-grade inflammation, and increased sympathetic activity, which are due to intermittent hypoxia.[8-10] The combination of these mechanisms leads to the formation of accelerated atherosclerosis. Patients with OSAS commonly have CVD risk factors such as obesity, hypertension, insulin resistance, and hyperlipidemia.[5,6,10,11] The prevalence of OSAS in patients with known hypertension is highly increased, 47% in males and 26% in females. However, Hedner et al[12] reported that according to their ambulatory home polysomnographic (PSG) study, there was OSAS in 25% and 24% of normotensive males and females, respectively. They studied 161 (77 male, 47.8%) patients with hypertension and 183 (97 male, 53%) normotensive patients having a mean body mass index (BMI) of 30 and 28.5 kg/m^2. Hence, OSAS in normotensive patients is of interest.

Noninvasive measurement of carotid artery systolic and diastolic diameter and intima–media thickness (IMT) by 2-dimensional ultrasonography and calculation of the carotid artery stiffness index are well defined and accepted in evaluation of atherosclerosis.[13,14]

Fetuin-A is a new biochemical marker, also known as α2-Heremans Schmid glycoprotein whose weight is 60 kDa.

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It is secreted from the liver and inhibits systemic calcification. Recently, fetuin-A has been shown to be inversely associated with atherosclerosis and inflammation.[15-17]

Although there has been much investigation of carotid IMT (cIMT) and arterial stiffness, there has been insufficient detailed investigation of serum fetuin-A levels in patients with OSAS. Therefore, we investigated whether there is a relationship between serum fetuin-A levels and cIMT and stiffness in normotensive and nondiabetic patients with OSAS.

Materials and Methods

Patients, Study Protocols, and Polysomnography

After approval of the study protocol by the ethics committee, this study was performed during a 14-month period between April 2012 and May 2013. The study used 88 patients (71 males and 17 females) aged 52 $\pm$ 8 years. In all, 50 patients had a diagnosis of OSAS with varying degrees of severity (22 mild, 7 moderate, and 21 severe). In all, 38 patients were diagnosed as non-OSAS. Patients were divided into 2 groups, OSAS and control. The study did not include patients on continuous positive airway pressure therapy. All study participants were evaluated by a cardiologist to exclude any CVD, such as CAD and hypertension. In all, 17 patients were diagnosed with dyslipidemia, n = 10 (20%) in the OSAS group and n = 7 (18.4%) in the control group. In all, 16 (32%) patients in the OSAS group were smokers, and 12 (31.5%) in the control group were smokers. We defined dyslipidemia as total cholesterol (TC) $\geq$200 mg/dL, low-density lipoprotein cholesterol (LDL-C) $\geq$130 mg/dL, triglycerides (TGs) $\geq$150 mg/dL, and high-density lipoprotein cholesterol (HDL-C) $\leq$40 mg/dL, as described previously.[18] None of the patients with dyslipidemia in either group was taking statins. There was no patient with metabolic syndrome in both the groups.

Exclusion criteria were as follows: hypertension, diabetes mellitus, medical treatment with antihypertensive, antidiabetic and lipid-lowering agents, congestive heart failure, bronchopulmonary infection, alcohol abuse, carotid artery stenosis of >50%, cerebrovascular disease, CAD, history of myocardial infarction, valvulopathy, renal or liver failure, and thyroid disorders.

Baseline characteristics such as age, gender, BMI, smoking, and hyperlipidemia were recorded for study and control groups. Fasting antecubital venous blood samples were collected to measure fasting glucose, TC, TG, HDL-C, LDL-C, creatinine, uric acid, fibrinogen, C-reactive protein (CRP), and fetuin-A. For fetuin-A measurement, plasma was stored in separate tubes at -80°C. Serum fetuin-A levels were measured using a human fetuin-A enzyme-linked immunosorbent assay (ELISA) kit (BioVendor Laboratory Medicine, Inc, Brno, Czech Republic) in an ELISA plate reader (ELX 800 Multi-Plate Reader; Bio-tek Instruments, Inc, Winooski, VT). The range of fetuin-A for healthy participants has not been defined by the manufacturer, but its minimum detectable concentration was 5 ng/mL. The measured intra-assay and interassay variability coefficients were 2.9% and 4.71%, respectively. Smith et al[19] reported poor agreement between plasma fetuin-A measurements made using different ELISA methods.

After obtaining informed consent from each patient, PSG findings were obtained using a computerized system (Embla N7000; Somnologica, Broomfield, Colorado). Respiratory parameters were analyzed automatically and then reexamined visually to ensure accuracy of the data. Cessation of airflow for $\geq$10 seconds was defined as apnea. A reduction in thoracic excursion of $\geq$50% for $\geq$ 10 seconds or oxygen desaturation of $\geq$3% was defined as hypopnea. Apnea hypopnea index (AHI) was calculated from the number of apnea and hypopnea events per hour of sleep. The numbers of respiratory and spontaneous arousals per hour were used as the arousal index. Those with an AHI score of $\geq$5 were put in the OSAS group.

Carotid IMT, Artery Stiffness, and Ankle-Brachial Index Parameters

After PSG study, all participants rested for 15 minutes before examination, and then, posterior wall cIMT was measured in a 1-cm segment in the first 2 cm below the common carotid artery bulb. Averaged cIMT values and systolic and diastolic diameters of the right and left common carotid arteries were calculated after measuring the cIMT, systolic, and diastolic diameters with a real-time scanner and a synchronized electrocardiogram (MyLab 50; Esaote, Genoa, Italy). Calculations were made using a 7.5-MHz linear array and semiautomated-guided technique radiofrequency-Quality IMT (Esaote, Maastricht, Holland). Two sequential measurements of systolic and diastolic brachial blood pressures (BPs) were recorded using an aneroid sphygmomanometer during measurements of carotid artery diameters. After the carotid artery studies, the BPs for the other arm and dorsalis pedis and posterior tibial artery systolic BPs in both the lower limbs were measured. To obtain systolic BP, an 8-MHz, continuous wave, hand-held, Doppler probe (Sonotrax-8 MHz Sonotrax Ultrasonic Vascular Pocket Doppler; Stork RADIO LLC, Boca Raton, Florida) was placed on the artery, the pneumatic cuff was inflated to at least 20 mm Hg above suprasystolic pressure, cuff pressure was gradually reduced, and the first sound heard was recorded as brachial systolic BP.

For the calculation of the ankle-brachial index (ABI), the higher systolic BP in the ankle was divided by the higher systolic BPs in the arm, and the lowest value was defined as the ABI. An ABI value <0.9 was assumed to represent peripheral arterial disease (PAD).[20]

Carotid artery stiffness (β) index was determined from changes (ΔD) in carotid artery diameters during the systole and diastole (D) simultaneously measured right-arm brachial artery pulse pressure (ΔP) according to the following formula: β (stiffness) index = ln(systolic pressure/diastolic pressure) $\times$ D/ΔD.

Increased carotid artery stiffness (β) index, decreased artery compliance, and artery strain are important determinants of

Table 1. Anthropometric, Clinical Features, and Biochemical Parameters of the Obstructive Sleep Apnea Syndrome (OSAS) and Control Groups.

	Patients With OSAS (n = 50)	Controls (n = 38)	*P*
Age, years	54.5 (33-64)	52 (43-65)	.816
Male, n (%)	41 (82)	30 (78.9)	.759[a]
Body mass index, kg/m^2	29.5 (23-44)	29.5 (22-42)	.944[b]
Current smoker, n (%)	16 (32)	12 (31.5)	.833[a]
Dyslipidemia, n (%)	10 (20)	7 (18.4)	.663[a]
Fasting glucose, mg/dL	81 (58-99)	78 (76-98)	.459[b]
Total cholesterol, mg/dL	162 ± 36	149 ± 32	.219[c]
Triglycerides, mg/dL	120 (59-148)	123 (54-149)	.622[b]
HDL cholesterol, mg/dL	38 (12-81)	41 (23-82)	.131[c]
LDL cholesterol, mg/dL	118 ± 34	122 ± 32	.723[c]
Creatinine, mg/dL	0.92 ± 0.33	0.76 ± 0.23	.444[c]
Uric acid, mg/dL	5 (2.4-7.7)	5 (3.6-8.5)	.742[b]
Fibrinogen, mg/dL	324 ± 71	283 ± 53	.01[c]
CRP, mg/dL	4.3 (0.1-6.1)	3.4 (0.1-5.5)	.166[b]
Fetuin-A, ng/mL	59.4 ± 6.5	68.2 ± 5.8	.029[c]

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein.
[a]Chi-square test.
[b]Mann-Whitney *U* test.
[c]Student *t* test.

Table 2. Comparison of Polysomnographic Findings and Vascular Parameters Between Patients With Obstructive Sleep Apnea Syndrome (OSAS) and Controls.

	Patients With OSAS (n = 50)	Controls (n = 38)	*P*
OSAS mild (AHI 5-15), n (%)	22	0	<.001[a]
OSAS moderate (AHI 16-30), n (%)	7	0	<.001[a]
OSAS severe (AHI > 30), n (%)	21	0	<.001[a]
AHI score	22.7 (6-81)	2 (1-4)	<.001[b]
Arousal index	28 (8-87)	11 (3-19)	<.001[b]
Lowest SaO2, %	69 ± 13	91 ± 5	<.001[c]
SaO_2 < 90%, PRTS	26 ± 14	1.1 ± 0.9	<.001[c]
Systolic blood pressure, mm Hg	125 (100-135)	125 (95-135)	.492[b]
Diastolic blood pressure, mm Hg	78 ± 7	79 ± 5	.401[c]
Carotid diastolic diameter, mm	7.3 ± 1.21	6.9 ± 0.85	.01[c]
Stroke change in diameter, mm	0.41 ± 0.23	0.34 ± 0.12	.001[c]
Carotid IMT, mm	0.73 ± 0.1	0.63 ± 0.1	<.001[c]
Carotid stiffness (β) index	7.45 ± 0.9	5.2 ± 0.7	.001[c]
Mean carotid plaque score	0.52 ± 0.2	0.49 ± 0.2	.146[c]
Ankle-brachial index	1.12 (1.02-1.48)	1.13 (1.03-1.47)	.498[b]

Abbreviations: AHI, apnea hypopnea index; IMT, Intima-media thickness; PRTS, Percentage of recording time spent at SaO_2 < 90%, mean arterial oxygen saturation below 90%.
[a]Chi-square test.
[b]Mann-Whitney *U* test.
[c]Student *t* test.

arterial stiffness that reflect arterial atherosclerosis. We only calculated the stiffness (β) index, because it is well defined and sufficient to evaluate elasticity of the arterial wall, as described previously.[21] We assumed that carotid arterial systolic and diastolic BP equate to brachial artery systolic and diastolic BP.

The cIMT, stiffness (β) index, and ABI measurements of 15 patients with OSAS were reexamined after 7 days to determine the coefficients of variation between visits. These were 3.5%, 4.9%, and 3.2% for cIMT, stiffness index, and ABI, respectively.

Statistical Analysis

Data were analyzed using the Predictive Analysis Software Statistics 18 (SPSS Inc, Chicago, Illinois). The Shapiro-Wilk normality test was used to check the variable distributions. To compare the 2 groups, 2 independent sample *t* tests were used for normally distributed variables, and the Mann-Whitney *U* test was performed for nonnormally distributed variables. A chi-square test was used to evaluate the categorical data. Categorical data such as gender, smoking, and dyslipidemia were expressed as numbers and percentages. *P* values <.05 (2-sided) were considered significant. Pearson and Spearman rank correlation tests were performed to assess whether there is a correlation between parametric and nonparametric variables, respectively, in the 2 groups. After univariate-independent variables were entered, multivariate regression analysis was performed to identify the determinants of cIMT and stiffness.

Results

Anthropometric, Clinical Features, and Biochemical Variables

The OSAS group included 50 patients aged 54.5 (33-64) years with a BMI of 29.5 (23-44) kg/m^2, 41 (82%) males and 9 (18%) females. The control group included 38 patients aged 52 (43-65) years with a BMI of 29.5 (22-42) kg/m^2, 30 (78.9%) male and 8 (21.1%) female. Age, gender, and BMI percentages of the 2 groups were similar ($P > .05$).

Smoking and dyslipidemia rates did not differ between the OSAS and the control groups (n = 16 [32%], n = 12 [31.5%], $P = .833$) and (n = 10 [20%], n = 7 [18.4%], $P = .663$). In addition, there was no difference between the 2 groups in terms of fasting glucose, TC, TG, HDL-C, LDL-C, creatinine, uric acid, and CRP levels (all values of $P > .05$). The OSAS group had higher fibrinogen (324 ± 71 vs 283 ± 53 mg/dL, $P = .01$) and lower fetuin-A levels (59.4 ± 6.5 vs 68.2 ± 5.8 ng/mL, $P = .029$) compared with the control group (Table 1).

Polysomnographic Values, Serum Fetuin-A, and Fibrinogen Levels

The AHI score (22.7 [6-81] vs 2 [1-4], $P < .001$), arousal index (28 [8-87] vs 11 [3-19], $P < .001$), and percentage of recording time spent (PRTS) of oxygen saturation (SaO_2) <90% (26 ± 14 vs 1.1 ± 0.9, $P < .001$) were significantly higher in the OSAS group. The lowest SaO_2 percentage values (69 ± 13 vs 91 ± 5, $P < .001$) were significantly lower in the OSAS group than in the control group (Table 2).

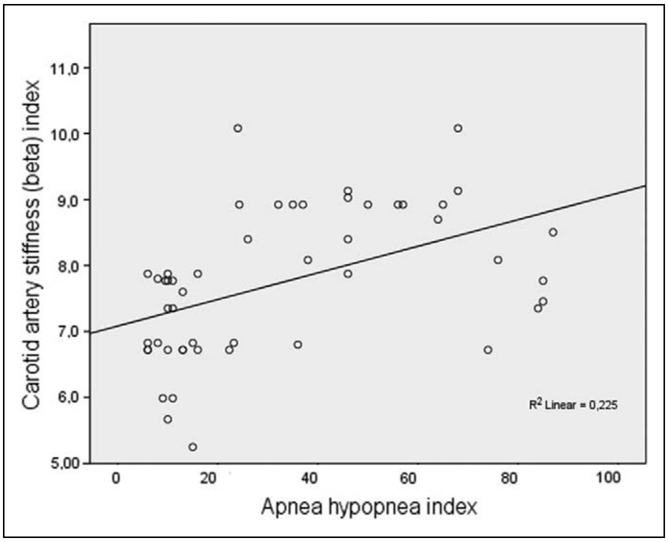

Figure1. The correlation between mean carotid artery stiffness (β) index and apnea hypopnea index ($r = .498$, $P < .001$).

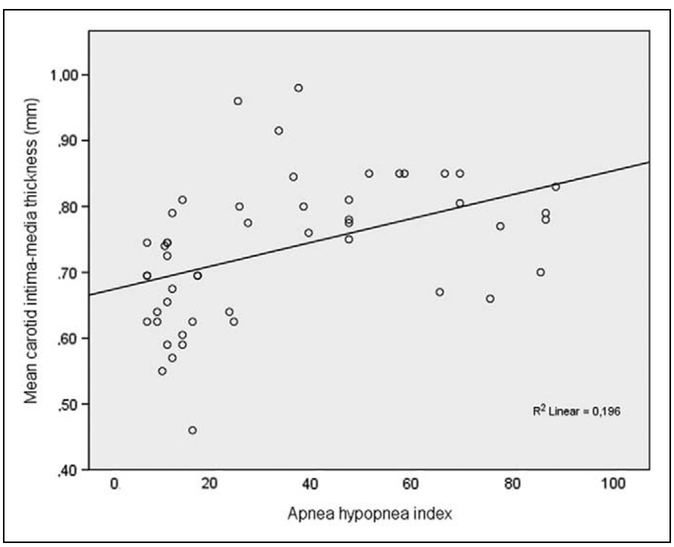

Figure 2. The correlation between mean carotid intima-media thickness and apnea hypopnea index ($r = .422$, $P = .001$).

The AHI and SaO_2 <90% of PRTS were negatively correlated with fetuin-A ($r = -.212$, $P = .044$) and fibrinogen levels ($r = .298$, $P = .034$), respectively.

Polysomnographic Values, Carotid Artery (β) Stiffness Index, cIMT, and ABI

No significant differences were seen in terms of systolic and diastolic BP values between the 2 groups (125 [100-135] vs 125 [95-135], $P = .492$ and 78 $\pm$ 7 vs 79 $\pm$ 5, $P = .401$, respectively). Compared with the control group, the OSAS group had a greater carotid diastolic diameter (7.3 $\pm$ 1.21 vs 6.9 $\pm$ 0.85 mm, $P = .01$), a significantly higher stroke change in diameter (0.41 $\pm$ 0.23 vs 0.34 $\pm$ 0.12 mm, $P = .001$), higher mean cIMT (0.73 $\pm$ 0.2 vs 0.63 $\pm$ 0.3 mm, $P < .001$), and higher carotid stiffness (β) index (7.45 $\pm$ 0.9 vs 5.2 $\pm$ 0.7, $P = .001$). Mean carotid plaque scores and ABI are similar between the groups (Table 2).

Table 3. Correlations between Polysomnographic Findings, Vascular Parameters, and Serum fetuin-A Levels.

	AHI		SaO_2 < 90%-PRTS	
	Coefficient	*P*	Coefficient	*P*
Carotid stiffness index	0.498	<.001[a]	0.341	.019[b]
Carotid IMT, mm	0.422	.001[a]	0.432	.001[b]
Ankle-brachial index	−0.133	.218[a]	−0.193	.074[a]
Fibrinogen	0.298	.034[a]	0.351	.01[b]
Fetuin-A	−0.212	.044[a]	−0.143	.185[b]

Abbreviations: AHI, apnea hypopnea index; IMT, Intima-media thickness; PRTS, percentage of recording time spent at SaO_2 < 90%; SaO_2, oxygen saturation.
[a]Spearman rank correlation test.
[b]Pearson correlation test.

Carotid artery stiffness (β) index and cIMT were positively correlated with AHI ($r = .498$, $P < .001$; $r = .422$, $P = .001$, respectively; Figures 1 and 2), and SaO_2 <90% of PRTS ($r = .341$, $P = .019$; $r = .432$, $P = .001$, respectively; Table 3) negatively correlated with fetuin-A ($r = -.324$, $P = .033$; $r = -.466$, $P < .001$; Figures 3 and 4) in the OSAS group. In addition, no correlation was found between Fetuin-A and ABI in the OSAS group ($r = -.139$, $P = .224$). Carotid artery stiffness (β) index, cIMT, and ABI were not correlated with fetuin-A in the control group (all P values >.05).

The ABI was not found to be correlated with AHI and SaO_2 <90% of PRTS. In addition, no correlation was found between serum fetuin-A levels and ABI values in either group ($P > .05$). A strong correlation between carotid artery stiffness and cIMT was found in both the groups.

To obtain potential determinants of carotid artery stiffness (β) index and cIMT, we entered age, BMI, AHI, SaO_2 <90% of PRTS, fibrinogen, and fetuin-A as independent variables in multivariate regression analysis. Carotid artery stiffness (β) index and cIMT were related to AHI (unstandardized $\beta = 0.02 \pm 0.04$, $P < .001$; unstandardized $\beta = 0.01 \pm 0.01$, $P = .003$, respectively) and age (unstandardized $\beta = 0.045 \pm 0.01$, $P < .001$; unstandardized $\beta = 0.004 \pm 0.01$, $P < .001$, respectively). No other variables were associated with carotid artery stiffness (β) index and cIMT (all $P > .05$).

Discussion

No detailed study has investigated the relationship between fetuin-A and carotid artery stiffness and cIMT in patients with OSAS. Furthermore, agreement on the normal range of fetuin-A in healthy participants is poor, because plasma fetuin-A measurements have been made using different ELISA methods.[19] We specifically investigated patients with OSAS who were normotensive and nondiabetic in a quest to determine how the

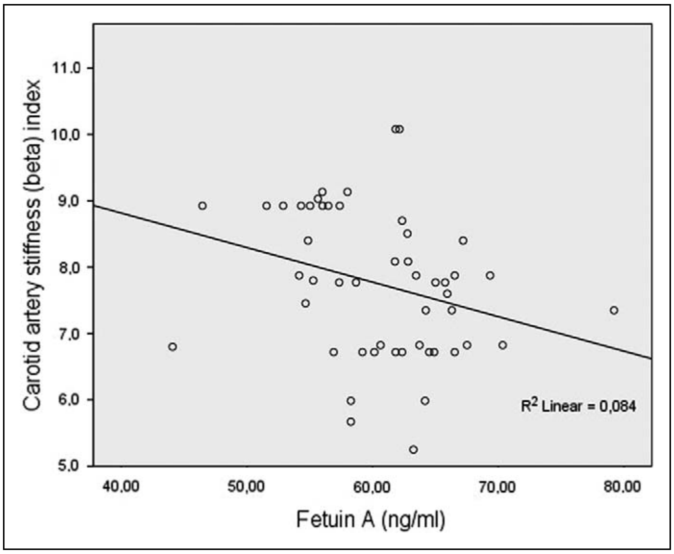

Figure 3. The inverse correlation between mean carotid artery stiffness (β) index and serum fetuin-A levels ($r = -.324$, $P = .033$).

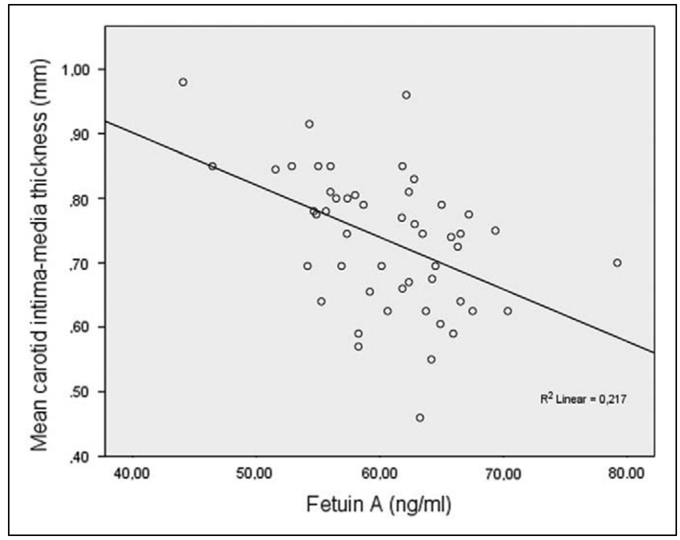

Figure 4. The negative correlation between mean carotid intima-media thickness and serum fetuin-A levels ($r = -.466$, $P < .001$).

association between OSAS and carotid artery stiffness and cIMT was affected by serum fetuin-A levels.

Our study yielded several findings. First, patients with normotensive and nondiabetic OSAS had significantly greater carotid stiffness and cIMT values, higher plasma fibrinogen levels, and lower serum fetuin-A concentrations than the control group. Second, carotid stiffness and cIMT positively correlated with AHI and SaO_2 <90% of PRTS and negatively with fetuin-A, and predictors of increased carotid stiffness and cIMT were age and AHI score in the OSAS group. Third, there was a negative relationship between fetuin-A and AHI. The ABI values of those with normotensive OSAS were similar to those with normotensive non-OSAS controls. There was no relationship between ABI values and serum fetuin-A concentrations.

Carotid IMT, an important indicator of future cardiovascular disorders, has been well studied in patients with OSAS,[22,23] but carotid stiffness has not. However, aortic stiffness in patients with OSAS has been evaluated.[23] Age and severity of OSAS have been found to predict increased carotid artery stiffness and cIMT.[22,23] These findings are similar to those of the current study. It is well documented that atherosclerotic risk factors, such as dyslipidemia, hypertension, and diabetes, are important predictors for increased carotid artery stiffness and cIMT.[24,25] In our study, no participants had diabetes or hypertension. In addition, none was taking lipid-lowering agents. We omitted the contributing effects of dyslipidemia to cIMT and stiffness; however, percentages of dyslipidemia were similar in both the groups. An association between decreased serum fetuin-A, a negative inflammatory marker, and increased cIMT and increased arterial stiffness has been reported.[26,27]

Although an increased cIMT commonly reflects early atherosclerosis,[13] a decreased ABI reflects a stenosis of >50% in major leg arteries,[28] and significant atherosclerosis[29] is associated with CAD. We specifically evaluated the ABI values to exclude PAD. The reason for all patients having normal ABI values in our study might be their normotensive and nondiabetic status.

In the present study, serum fibrinogen levels correlated with AHI and SaO_2 <90% of PRTS as reported by Wessendorf et al.[30] Increased fibrinogen levels are responsible for increased cardiovascular embolic events in patients with OSAS.[30] The other contributors for stroke are endothelial dysfunction as well as increased hematocrit, blood viscosity, coagulation activity, and platelet activity, which occur due to intermittent hypoxia.[31] However, we did not investigate these variables, because their contributions in OSAS have been well documented.

There has been no detailed study of serum fetuin-A levels in patients with OSAS until the present study, which showed lower levels in the OSAS group than in the controls, possibly as a result of the mild inflammation triggered by intermittent hypoxia. Although a number of studies have claimed serum fetuin-A as a negative acute-phase reactant with anti-inflammatory effects,[17,32] others have reported a positive correlation with increased atherosclerosis.[33,34] We found that fetuin-A is a negative inflammatory marker for the presence and severity of OSAS and atherosclerosis. In contrast, Mori et al[34] concluded that increased fetuin-A was associated with increased carotid artery stiffness. There is a need for future studies that use identical ELISA methods so that their results can be compared to determine whether fetuin-A deficiency may contribute to increased carotid artery stiffness and cIMT.

The main limitation of our study is the small number of patients with OSAS. We particularly recruited normotensive, nondiabetic, and non-CAD patients in the OSAS group. If we had enrolled patients with OSAS who had hypertension, diabetes, and CAD, we could have included more patients. Second, we used brachial systolic and diastolic BP values to calculate β stiffness index; it would be better to use local pulse pressure obtained by tonometry. Third, if we had studied other inflammatory mediators and markers, such as serum tumor necrosis factor (TNF), some interleukins (IL-1 and IL-6), interferon gamma, and growth factors, serum C3, C4, and high sensitivity CRP, they could have validated our findings further.

In conclusion, increased carotid artery stiffness and cIMT are associated with lower fetuin-A levels, higher fibrinogen levels, and higher AHI as well as with increased age in normotensive and nondiabetic patients with OSAS. There is a need for larger studies to investigate the contribution of the serum inflammatory markers such as IL-6 and TNF, as well as fetuin-A, to atherosclerosis in patients with OSAS.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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