Influence of obstructive sleep apnea on ischemia-modified albumin levels and carotid intima-media thickness

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ABSTRACT

Obstructive sleep apnea (OSA) is associated with an increased risk of atherosclerosis. Carotid intima-media thickness (CIMT) is strongly associated with the presence of significant risk factors for cardiovascular disturbances. A disturbance in the oxidative/antioxidative balance is involved in the pathogenesis of OSA and cardiovascular diseases. Ischemia-modified albumin (IMA) is suggested as a novel marker of oxidative stress; IMA can be defined as decreased binding of transitional metal ions to serum albumin in oxidative status. The purpose of this research was to evaluate the influence of OSA on IMA levels and CIMT. In total, 61 individuals with OSA with no comorbidities and 24 healthy controls with a similar body mass index and age were enrolled in this study. Serum levels of IMA, CIMT (estimated radiologically), and polysomnographic parameters, were determined and interpreted. Serum IMA levels were significantly higher in individuals with OSA compared with the control group (p=0.0003). CIMT was significantly higher in the OSA group compared with the control group (0.88± 0.26 mm vs 0.75±0.17 mm, p=0.005). The CIMT and serum IMA levels were positively correlated with the apnea-hypopnea index (r=0.35 and r=0.32, respectively), and with the oxygen desaturation index (r=0.34 and r=0.29, respectively) at baseline. Increased IMA levels and CIMT may be related to increased oxidative stress and risk of atherosclerosis in individuals with OSA.

Significance of this study

What is already known about this subject?

- Obstructive sleep apnea is associated with an increased risk of atherosclerosis.
- Ischemia-modified albumin is suggested as a novel marker of oxidative stress.
- Carotid intima-media thickness is strongly associated with the presence of significant risk factors for cardiovascular disturbances.

What are the new findings?

- Serum IMA levels were significantly higher in individuals with OSA compared with the control group.
- CIMT was significantly higher in the OSA group compared with the control group.
- The CIMT and serum IMA levels were positively correlated with the apnea-hypopnea index and oxygen desaturation index.

How might these results change the focus of research or clinical practice?

- Measuring CIMT could be beneficial as an everyday application because it is easy to determine, noninvasive, and can be assessed repeatedly.
- Serum levels of IMA can be used as a novel marker of oxidative stress in OSA.

INTRODUCTION

Obstructive sleep apnea (OSA) has become an increasingly recognized health problem with evidence suggesting that untreated OSA may cause an increased risk of various cardiovascular disorders. OSA is a widespread disorder characterized by periodic obstructions of the upper airways during sleep, which induces apnea and hypopnea events that are responsible for recurrent desaturation–reoxygenation sequences. The link between OSA and cardiovascular disease (CVD) has been previously described.[1] Experimental research has demonstrated that oxygen desaturation due to apneic conditions leads to disruptive alterations at the level of the arterial wall, which may be involved in the connection between OSA and atherosclerosis.[2]

The suggested mechanism of atherosclerosis in OSA involves increased oxidative stress. Oxidative stress is known to be detrimental to the vascular endothelium; to stimulate atherosclerosis; and to lead to adverse cardiovascular conditions.[3] One important mechanism by which OSA may support atherosclerosis is intermittent hypoxia (IH), in which patients are exposed to recurrent episodes of short oxygen desaturation in the blood, followed by reoxygenation. Similarly, cycles of hypoxia/reoxygenation may cause the overproduction of reactive oxygen species (ROS). Oxidative stress plays an important role in the pathogenesis of OSA. Increased production of ROS is known to be related to the pathogenesis of atherosclerosis, and may explain the increased rates of

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CVD seen in OSA.[4] Ischemia-modified albumin (IMA) has been suggested previously as a novel marker of ischemia, which is determined using the albumin cobalt binding test (in turn based on the formation of a colored complex from unbound cobalt ions due to the decreased binding of transitional metal ions to serum albumin). [5] Recently, IMA has been found to be related to increased oxidative stress, and may be a potential cardiovascular risk factor; research has indicated a possible relationship between IMA and other cardiovascular risk factors, and diseases with higher incidences of vascular events.[6–8] Sleep apnea syndrome is a multifactor disease characterized by increased respiratory efforts, IH and sleep fragmentation. In rodents, IH has been suggested to imitate one of the outcomes of sleep apnea. As a particular type of sleep apnea, IH has been shown to have an effect on atherogenesis, detecting changes in tissue and plasma that may contribute to the development and advancement of atherosclerosis. CIMT is beneficial as a substitute marker of early endothelial deficiency and as a marker of subclinical or early atherosclerosis development. A CIMT of ≥0.75 mm is related to a higher risk of CVD.[9] However, it has not yet been investigated whether OSA itself may be the cause of noninvasive CIMT. CIMT is well demonstrated by ultrasonography and has known utility for the assessment of atherosclerosis.[8] Moreover, enhanced CIMT in individuals suffering from sleep apnea compared to healthy participants has been documented extensively.[10]

The effect of OSA on the action of IMA is poorly understood. Although a potential role for IMA in clinical disorders other than OSA has been shown, the effect of apnea-related hypoxia on this biomarker has not been determined. Furthermore, the relationship between oxidative stress biomarkers of atherosclerosis and CIMT has not been analyzed extensively in patients with OSA. Therefore, the purpose of this research is to assess the relationship between oxidative stress markers and the risk of developing atherosclerosis in patients with OSA, by assessing IMA levels and CIMT. We also aim to demonstrate whether these markers could be used to predict cardiovascular risk.

METHODS

This research used a prospective case-control design. We enrolled 85 patients (32 females and 53 males) who were admitted to Mevlana University Hospital. Our research protocol was approved by the Clinical Research Ethics Committee of Mevlana University and the study procedures were undertaken at Mevlana University Hospital.

Study group

This prospective study included 61 patients (23 females, 38 males; mean age, 53.5±11.2 years) who were admitted to the sleep laboratory of our hospital with complaints of apnea, snoring, or daytime sleepiness and in whom polysomnography (PSG) had been performed between January 2015 and June 2015; 24 matched healthy controls (body mass index (BMI)± 2 kg/m^2 and age± 3 years) were also enrolled (9 females, 15 males; mean age, 50.0±11.5 years).

All participants were monitored overnight at the sleep unit, using PSG, and 61 cases were diagnosed as OSA with varying levels of severity (19 mild, 14 moderate, and 29 severe). The 24 control group participants were confirmed as non-OSA by PSG. Written informed consent was obtained from all participants. Health behavior-associated and demographic data—including sex, age and BMI—were gathered from the patient records.

Participants with a serum albumin level <2 g/dL or >5.5 g/dL; chronic or acute conditions that might influence IMA levels and CMIT (ischemic heart disease, diabetes mellitus, mesenteric ischemia, peripheral vascular disease, ischemic cerebrovascular disease, liver disease, pulmonary embolism, muscle diseases, systemic infections at or within 2 weeks of study participation, or use of any antioxidant drugs that could affect the outcomes); and cases who did not want to participate in the research, were excluded (figure 1).

Evaluation of risk components

A medical history was obtained from all participants, in addition to a full physical examination, and BMI values were calculated. Blood samples were taken from all participants to assess lipid and glucose levels. Participants with no history of cardiovascular disorders (hypertension, coronary artery disease) or substantial abnormalities (hyperlipidemia or hyperglycemia) identified by laboratory tests were enrolled in the further stages of the research.

The following information was registered for every subject: gender, age, medical history, and smoking and alcohol consumption. We classified participants who smoked one or more cigarettes per day as smokers, and excluded smokers and alcohol-consuming participants. None of the control participants used lipid- or blood pressure-lowering medications or antidiabetic drugs.

Sample collection and analysis

After fasting for a minimum of 8 h, venous blood samples were obtained from the antecubital veins of all participants between 8.00 am and 9.00 am. Blood specimens were centrifuged at 1000 g for 10 min at room temperature to separate the serum. Aliquots of the serum were transferred into polyethylene tubes and utilized in the analysis of biochemical factors. The samples were stored at −40°C until analysis.

Ischemia-modified albumin

IMA levels were determined by a colorimetric assay, as previously described by Bar-Or *et al*.[11] Albumin analysis was performed with a Cobas albumin reagent based on the bromocresol green method (Cobas, Roche Diagnostics, USA). The formula suggested by Lippi *et al*[12] was applied to adjust the IMA values according to the serum albumin levels, as follows:

$$\text{Albumin} - \text{adjusted IMA level} = [(\text{individual serum albumin concentration}/\text{median albumin concentration of the population}) \times \text{IMA value} \times \text{IMA value}]$$

IMA and albumin-adjusted IMA levels were expressed in absorbance units (ABSU).

Determination of CIMT

The bilateral common carotid arteries of all participants were scanned longitudinally with a 7 MHz transducer

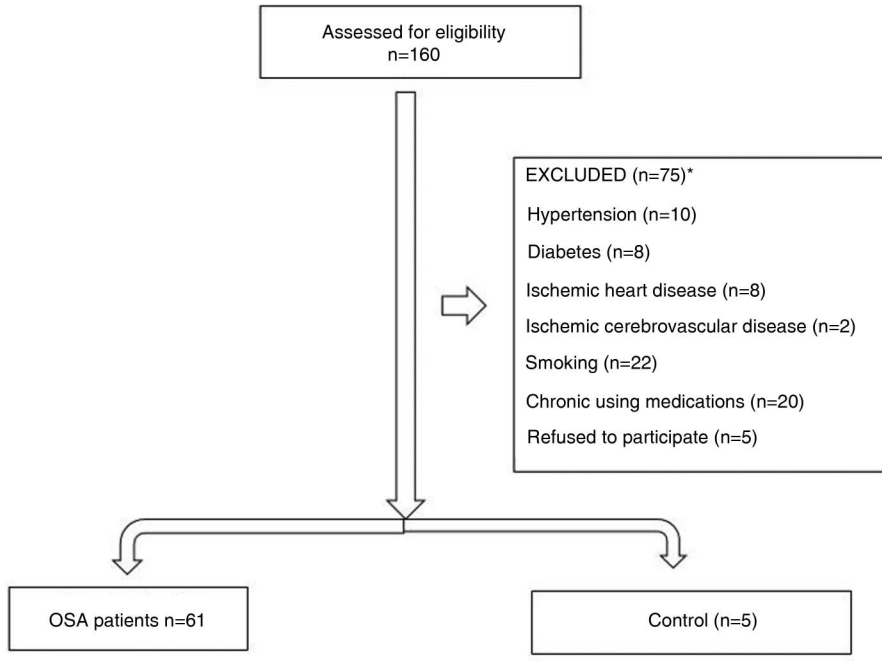

Figure 1 Flow diagram of the progress through the phases of the study. *Some patients had multiple exclusion.

attached to an Aloka 5000 device (Aloka Co, Ltd, Tokyo, Japan). Images of the distal section of the common carotid artery were obtained, 1–2 cm proximal to the carotid bulb. The two bright echogenic lines in the arterial wall were the intima and media lines. The intima-media thickness was measured as the distance from the primary margin of the first echogenic line to the main margin of the second echogenic line. All measurements were performed by the same radiologist. Images displaying the greatest intima-media thickness were digitally stored and CIMT measurements made offline. The intima-media thickness of the distal wall of the right common carotid artery on the longitudinal axis was calculated using the procedure of Pignoli *et al*.[13] Every measurement was repeated three times, and the average of the right and left common carotid artery values was used in the analysis. The cIMT measurements of OSAS patients were determined and the coefficient of variation was 3.5%. Plaques characterized by >50% localized thickening of the intima compared to the rest of the wall—or endoluminal protrusion of the arterial lumen of >0.5 mm—were not included in the measurement of CIMT.

Statistical analysis

The data were statistically evaluated using SPSS for Windows software (V.15.0; (SPSS Inc, Chicago, Illinois, USA). The distribution pattern was evaluated with the Kolmogorov-Smirnov test. For intergroup comparison, the Mann-Whitney U test was used. Non-parametric Spearman's correlation analysis was used to evaluate the relationships between sleep severity index score, biochemical parameters and CIMT. The χ^2 test was used to compare the categorical data. Multiple regression was performed to identify independent predictors of CIMT. A p value <0.05 was considered statistically significant.

RESULTS

The demographic data of the participants with OSA and the control participants, including age, gender, BMI, apnea-hypopnea index (AHI), oxygen desaturation index (ODI), mean arterial oxygen saturation (SaO_2), and total sleep time with oxyhemoglobin saturation below 90% (TST90), are listed in table 1.

CIMT was significantly increased in participants with OSA compared to the control participants (0.88±0.26 mm vs 0.75±0.17 mm, p=0.005). The mean IMA levels of patients with OSA (1.231±0.102) were significantly higher

Table 1 Demographic characteristics and polysomnographic evaluation of OSA and control groups

	OSA	Control	p Value
Patients (n)	61	24	
F/M	23/38	9/15	NS
Age (years)	51.2±9.9	49.1±10.1	NS
BMI (kg/m²)	32. 3±3.5	30.3±5.3	NS
SBP, mm Hg	118±13.0	116±12.1	NS
LDL (mg/dL)	113±25.4	93±31.1	NS
Triglycerides (mg/dL)	134±60.4	114±48.2	NS
AHI (events/h of sleep)	35.9±26.7	3.0±1.8	<0.05
ODI (events/h)	42.7±34.8	4.2±3.4	<0.05
TST90	107.9±1402	20.4±49.9	<0.05
Mean SaO2 (%)	90.2±6.0	93.7±2.6	<0.05

Data are numbers or means±SD.
TST90, total sleep time with oxyhemoglobin saturation below 90%, significantly different from healthy controls (p<0.05, non-paired t test).
AHI, apnea-hypopnea index; BMI, body mass index; F, female; LDL, Low-density lipoprotein; M, male; mean SaO_2, mean of arterial oxygen saturation; NS, not significant; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; SBP, systolic blood pressure.

Table 2 Serum levels of IMA and CIMT values in OSA and control groups

Marker	OSA	Control	p Value
IMA (ABSU)	1.231±0.102	1.088±0.156	0.0003
cIMT (mm)	0.88±0.26	0.75±0.17	0.005
Albumin (g/dl)	4.95±0.32	4.89±0.38	>0.05

Data are presented as means±SD.
p Values were calculated by Mann-Whitney U-tests.
CIMT, Carotid intima–media thickness; IMA, Ischemia-modified albumin; OSA, obstructive sleep apnea.

Table 3 Spearman correlation between IMA, CIMT and age, BMI, and OSA severity index parameters

Variables	Age	BMI	AHI	ODI	Mean SaO2	TST90	Albumin
IMA	0.07	0.12	0.32	0.29	−0.09	0.19	−0.21
CIMT	0.04	0.05	0.35	0.34	−0.22	0.29	

AHI, apnea-hypopnea index; BMI, body mass index; cIMT, carotid intima-media thickness; IMA, ischemia modified albumin; mean SaO2, mean of arterial oxygen saturation; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; TST90, total sleep time with oxyhemoglobin saturation below 90%.

compared to the levels of the control participants (1.088 ±0.156, p=0.0003; table 2, figure 2A, B).

There was no significant correlation between the serum IMA levels and age (r=0.03, p>0.05) or BMI (r=0.17, p>0.05). However, there was a correlation between the IMA levels, and AHI (r=0.32, p=0.004) and ODI scores (r=0.29, p=0.01). There was no significant correlation between serum IMA levels and mean SaO_2 (r=−0.09; p>0.05) or TST90 (r=0.19; p>0.05) value. CIMT was significantly correlated with AHI (r=0.35; p=0.001), ODI (r=0.34; p=0.001) or TST90 (r=0.29) value scores. There was no significant correlation between CIMT and age, BMI, or mean SaO_2 (table 3).

To assess whether any association between CIMT and AHI was independent of age, gender and BMI, multiple regression was performed. After adjustments, CIMT was still significantly associated with AHI and yielded an estimated elevation in AHI of β=0.420 (p<0.001) per unit increase. No other variables were associated with CIMT (all p>0.05; table 4).

DISCUSSION

Research supports the notion that serum IMA is an oxidative stress marker that affects inflammatory responses[14] and, furthermore, that there is a positive relationship between higher IMA levels and an increased risk of atherosclerosis.[15] Based on the above results, it could be hypothesized that elevated serum IMA concentrations and increased CIMT reflect chronic oxidative stress in OSA. However, to date, there has been no comprehensive investigation of serum IMA levels and CIMT in individuals with OSA. The present study addresses this gap, showing elevated levels of IMA in the OSA group compared with the control group, and activation of the inflammatory response as a consequence of IH. In particular, we analyzed participants with OSA who were nondiabetic and normotensive, to determine how the relationship between OSA and CIMT was influenced by serum IMA.

In this study, we showed that:

1. CIMT in the OSA group was significantly higher than in the control group (0.88 mm vs 0.75 mm, p<0.05).
2. Serum IMA levels were significantly higher in the OSA participants compared with controls and CIMT was not correlated with IMA level.
3. There was a significantly stronger association between OSA severity index parameters (AHI and ODI scores), and IMA and CIMT values, in OSA participants compared with controls.

OSA is associated with significantly higher morbidity and mortality due to cardiovascular incidents. Although cardiovascular and OSA disorders share numerous risk factors, epidemiological research has shown that OSA is an independent and significant risk factor for the development of atherosclerosis.[16] In our study, we applied representative measures of atherosclerosis, such as CIMT, that have been used previously for the evaluation of endothelial function.[15] Previous reports have suggested that CIMT is associated with variations in vascular morphology;[8] measuring CIMT could be beneficial as an everyday application because it is easy to determine, noninvasive, and can be assessed repeatedly. Increased CIMT is not synonymous with atherosclerosis, but the primary pathophysiological

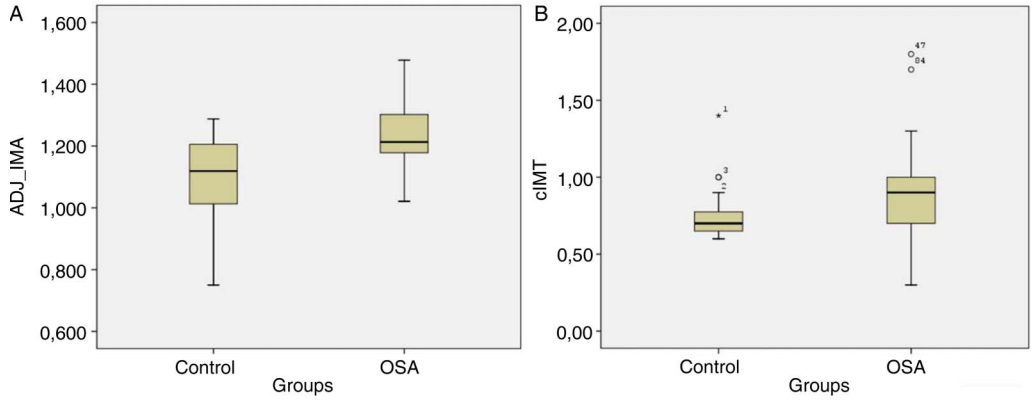

Figure 2 IMA levels and CIMT in OSA and control groups (figure 2A p value: 0.0003 and figure 2B p value: 0.005). IMA, ischemia-modified albumin; cIMT, carotid intima-media thickness; OSA, obstructive sleep apnea.

Table 4 Multiple linear regression models for associations with cIMT (as dependent variable) adjusting for age, BMI, gender, and AHI (as independent variable) in patients; regression coefficients (β), SE of b (SE β) and t statistic with corresponding p value

Variable	β coefficient	SE β	t statistic	p Value
Age	−0.001	0.003	−0.361	0.71
Gender	0.058	0.006	1.095	0.27
BMI	−0.006	0.053	−0.920	0.36
AHI	0.420	0.001	4168	**0.001***

*Statistically significant results are shown in bold.
AHI, apnea-hypopnea index; BMI, body mass index; cIMT, carotid intima-media thickness.

mechanisms are similar between the two conditions.[13] Ciccone *et al*[17] reported a positive relationship between CIMT and the duration of OSA. Increased CIMT is related with high risk CVDs,[18] cardiovascular incidents[19] and more serious coronary atherosclerosis.[20] However, the mechanism underlying these associations remains to be fully elucidated.

Many hypotheses have been suggested to account for endothelial dysfunction: oxidative stress appears to underlie endothelial impairment in individuals with OSA,[21] and it has also been confirmed that OSA causes endothelial dysfunction.[22] The two basic mechanisms underlying the abnormal vascular endothelial changes observed in OSA participants are recurrent episodes of hypoxia/reoxygenation—related to temporary interruption of breathing during sleep—and sleep fragmentation/deficiency.[23] Both of these mechanisms lead to systemic inflammation, indicated by enhanced levels of different inflammatory biomarkers.[23] The continuing effects of inflammatory reactions are partly responsible for atherosclerosis.[24]

OSA leads to recurrent hypoxic episodes and reoxygenation on waking. Many reports state that this desaturation—and the subsequent reoxygenation period—cause oxidative stress, generating ROS.[25] Elevated ROS levels eventually cause systemic inflammation.[26] Additionally, recent in vitro research has shown that the cascade of proinflammatory reactions that cause the generation of ROS (eg, hydroxyl radicals generated by the Fenton reaction) are related to a rapid increase in serum IMA levels.[7] When the normal balance is skewed towards oxidants, endothelial cells exposed to oxidative stress become more vulnerable to damage from these hydroxyl radicals. Additionally, hypoxia activates hypoxia-inducible factor l-a, consequently causing angiogenesis.[27] The oxidative balance is disrupted in patients with OSA, which causes increased generation of proinflammatory cytokines. As demonstrated previously, the highly sensitive C reactive protein, which is one of the most significant and common determinants of inflammation, is substantially increased in individuals with OSA and a CIMT >0.65 mm. CIMT has been shown to be associated with various biochemical markers, such as C reactive protein,[28] interleukin-6,[28] and total cholesterol.[29]

Albumin demonstrates structural alterations in response to environmental modification in the serum, including increased ROS. Albumin is an important and dominant antioxidant in plasma.[30] One of the main markers of increased oxidative stress in OSA is enhanced ROS production, which leads to increased protein oxidation. Structural modifications in the N-terminus of serum albumin are caused by the generation of ROS during ischemia, which changes the molecule into IMA.[11] IMA is a poorly understood and nonspecific determinant that is elevated during oxidative stress due to ischemia. In previous studies, elevated serum IMA has been linked to cerebrovascular events,[31] mesentery ischemia,[32] venous thromboembolism,[33] pulmonary embolism,[34] carbon monoxide poisoning,[35] and ischemia in the extremities.[36] Previous research has also demonstrated significantly higher IMA levels in type 2 diabetes mellitus,[37] metabolic syndrome and hyperlipidemia,[14] end-stage renal disease, thyroid dysfunction, and seasonal allergic conjunctivitis.[38–40] Accordingly, it has been suggested that increased levels of IMA might reflect a generalized rather than tissue-specific or organ-specific condition of oxidative stress. In this, increase of oxidative stress conditions with relation to chronic hypoxia is the most likely cause of modifications in the N-terminus of serum albumin and, subsequently, increased IMA levels in patients with OSA. There are only two reports discussing IMA levels in patients with OSA. Yang *et al*[41] demonstrated elevated IMA levels in OSA as well as a strong positive correlation between IMA and AHI scores. However, Ozben *et al*[42] stated that the IMA levels of patients with OSA were not different from those of healthy controls. In our clinical case–control study, serum IMA levels in participants with OSA were significantly increased compared to those of controls. We also observed a correlation between IMA levels and AHI and ODI scores. Therefore, our results are in agreement with Yang *et al*.

Another factor associated with endothelial abnormalities is sleep fragmentation/deficiency. In this study, a relationship between CIMT and AHI was detected. This suggests that sleep fragmentation due to intermittent apnea-hypopnea results in inflammation and metabolic dysregulation, which, in turn, lead to vascular pathology. Suzuki *et al*[29] reported that common carotid artery-IMT was associated with AHI. The relationship between OSA-related hypoxemia and CIMT is independent from AHI, showing that hypoxia can be an independent risk factor for arterial wall lesions. Importantly, the participants in this study had several comorbidities other than tobacco smoking (arterial hypertension, 47.3%; dyslipidemia, 18%; and diabetes mellitus, 17.4%) that can affect CIMT.[32] However, even after adjusting for confounding variables, the correlation between OSA and IMT remained. This result showed that significant vascular atherosclerotic risk factors, such as hypertension, diabetes, and dyslipidemia, are independent predictors of CIMT.[43] In our study, we excluded participants with comorbidities (such as dyslipidemia, diabetes mellitus, hypertension and smoking) because these factors were identified as confounders in previous research. Furthermore, none of our participants were receiving antihypertensive or lipid-lowering agents, discounting the possibility of an influence of dyslipidemia on CIMT.

In another study, Wattanakit *et al*[44] showed no relationship between CIMT and atherosclerosis on the respiratory disturbance index (RDI) after controlling for additional risk factors for atherosclerosis in 985 individuals drawn from the general population. Significantly, their patients had

different risk factors for CVDs and were suffering from mild-to-moderate OSA with an average RDI of 8.7 events/h. By contrast, our patients did not have any known comorbidities. Three small case control studies (n<35) showed that patients with severe OSA had significantly greater CIMT and more carotid plaques than matched controls.[10 45 46] Similarly, cross-sectional research showed that patients with severe OSA had considerably greater CIMT than those with habitual snoring but only mild OSA (RDI < 5 events/h).[29]

In the present study, ODI showed a significantly stronger association with CIMT in the OSA participants compared with the control participants. In a previous report,[47] the severity of oxygen desaturation was the main predictor of atherosclerotic plaques and CIMT formation in 83 individuals with OSA. Our research demonstrated that IMA increased commensurate with increases in AHI or ODI scores.

Comparing the present data on CIMT and IMA levels with those of previous research is difficult, as they differ with respect to the study populations and methodologies. Most of the previous studies included typical OSA populations, that is, patients who had a number of medical comorbidities. Therefore, they could not confirm that OSA alone was the cause of atherosclerosis and serum inflammatory markers; any of the risk factors, but especially diabetes, hyperlipidemia, and hypertension, may have influenced the results. In our study, there was no significant difference between the groups in terms of age, gender or BMI, and patients with hypertension, hyperlipidemia, and diabetes, were excluded from the research. Under these conditions, we showed that CIMT and serum IMA levels were significantly higher in patients with OSA compared with controls having normal AHI scores. Therefore, we showed a clear association between OSA, CIMT and IMA levels.

Several limitations of our study should be mentioned. First, our sample size was small, which might have been responsible for weak correlations among some of the factors. We especially recruited nondiabetic, normotensive, and non-ischemic heart disease patients in the OSA group. If we had enrolled individuals with OSA who had diabetes, hypertension, and ischemic heart disease, we could have included more patients. Larger scale studies should be performed to further evaluate and confirm the relationship between IMA and oxidative stress in OSA.

In conclusion, we suggest that serum levels of IMA can be used as a novel marker of oxidative stress in OSA. Measurement of CIMT could be used to assess the extent of atherosclerotic progression in patients with OSA. The clinical implication of this research is that individuals with recently diagnosed OSA, but no known comorbidities, may already be showing increased CIMT. Our results indicate that regular assessment for the development of atherosclerosis should be started in such cases.

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