Serum YKL–40/chitinase 3–like protein 1 level is an independent predictor of atherosclerosis development in patients with obstructive sleep apnea syndrome

Obstrüktif uyku apne sendromlu hastalarda serum YKL–40/kitinaz 3–benzeri protein 1 düzeyi ateroskleroz gelişiminin bağımsız bir öngörücüsüdür

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ABSTRACT

Objective: The inflammatory process plays an important role in the development of cardiovascular complications in patients with obstructive sleep apnea syndrome (OSAS). YKL-40/chitinase 3–like protein 1 is a novel biomarker of systemic inflammation. This study aimed to investigate whether carotid intima-media thickness (CIMT), a useful marker for early atherosclerosis, is associated with serum YKL–40/chitinase 3–like protein 1 levels in patients with normotensive and nondiabetic OSAS.

Methods: The study included 40 OSAS patients and 40 age- sex- and body mass index-matched healthy controls. Serum YKL–40 levels were detected by enzyme-linked immunosorbent assay. CIMT was measured by B-mode ultrasound.

Results: The patients with OSAS had significantly increased CIMT and higher YKL–40 and high sensitivity C-reactive protein (hsCRP) levels than those of the controls. CIMT was strongly correlated with serum YKL–40 levels (r=0.694, p<0.001), hsCRP (r=0.622, p<0.001), age (r=0.525, p=0.001), and weakly correlated with apnea-hypopnea index (AHI) (r=0.365, p=0.021) and the percentage of recording time spent (PRTS) of oxygen saturation <90% (r=0.488, p=0.001). Moreover, it was detected that serum YKL-40 levels were strongly correlated with AHI (r=0.617, p<0.001), and weakly correlated with SaO_2 <90% of PRTS (r=0.394, p=0.012) and hsCRP (r=0.486, p=0.001). In multiple regression analyses, age and serum levels of YKL–40 and hsCRP were found to be independent predictors of CIMT.

Conclusion: In patients with OSAS, CIMT was increased. This increase was associated with serum YKL–40 level. Increased serum level of YKL–40 may be an early predictor of atherosclerosis development in patients with OSAS.

ÖZET

Amaç: Enflamatuvar süreç obstrüktif uyku apne sendromu (OUAS) bulunan hastalarda kardiyovasküler komplikasyonların gelişmesinde önemli bir rol oynar. YKL–40/kitinaz 3–benzeri protein 1 sistemik enflamasyonun güncel bir belirtecidir. Bu çalışmada, erken ateroskleroz için faydalı bir belirteç olan karotis intima medya kalınlığının (KİMK) diyabeti olmayan normotansif OUAS'li hastalarda serum YKL–40/Kitinaz 3–benzeri protein 1 düzeyleri ile ilişkisi araştırıldı.

Yöntemler: Çalışmaya OUAS'li 40 hasta ile yaş, cinsiyet ve beden kütle indeksi açısından eşleştirilmiş 40 sağlıklı kontrol alındı. Serum YKL–40 düzeyleri enzim bağlı immünosorbent ölçüm yöntemi ile belirlendi. KİMK, B-mod ultrason ile ölçüldü.

Bulgular: OUAS'li hastalar, kontrole göre önemli ölçüde artmış KİMK ve daha yüksek YKL–40 ve yüksek duyarlıklı C-reaktif protein (hsCRP) düzeylerine sahipti. KİMK; serum YKL–40 düzeyleri (r=0.694, p<0.001), hsCRP (r=0.622, p<0.001) ve yaş (r=0.525, p=0.001) ile güçlü bir şekilde, apne-hipopne indeksi (AHİ) (r=0.365, p=0.021) ve %90 altındaki ortalama oksijen satürasyon süresinin yüzdesi (r=0.488, p=0.001) ile zayıf bir şekilde ilişkili idi. Ayrıca serum YKL–40 düzeylerinin AHİ (r=0.617, p<0.001) ile güçlü bir şekilde, %90 altındaki ortalama oksijen satürasyon süresinin yüzdesi (r=0.394, p=0.012) ve hsCRP (r=0.486, p=0.001) ile zayıf bir şekilde ilişkili olduğu tespit edildi. Çoklu regresyon analizinde, yaş, serum YKL–40 ve hsCRP düzeylerinin KİMK'nin bağımsız öngördürücüleri olduğu bulundu.

Sonuç: OUAS'li hastalarda KİMK artmıştır. Bu artış serum YKL–40 düzeyi ile ilişkilidir. OUAS'li hastalarda artmış serum YKL–40 düzeyi ateroskleroz gelişiminin erken öngörücüsü olabilir.

Received: October 11, 2014 *Accepted:* December 16, 2014

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Obstructive sleep apnea syndrome (OSAS) is a common sleep-related breathing disorder, and is associated with several cardiovascular disturbances such as coronary artery disease (CAD), congestive heart failure, hypertension, cardiac arrhythmias, stroke and pulmonary hypertension.[1]

YKL–40, also known as human cartilage glycoprotein-39 and chitinase-like protein 1, is a 40 kDa heparin- and chitin-binding glycoprotein and a member of the "mammalian chitinase-like proteins".[2,3] YKL–40, an inflammatory marker in relation to both acute and chronic inflammation and with an established role in extracellular remodelling remodeling and angiogenesis, is secreted from macrophages, neutrophils and vascular smooth muscle cells (VSMCs).[4] YKL–40 is closely related to both early and late phases of the atherosclerotic process. Several studies have shown that serum concentrations of YKL–40 are elevated in patients with CAD, and that there is an association between serum YKL–40 levels and the extent of CAD.[5,6]

Carotid intima-media thickness (CIMT) is frequently used as a surrogate marker for subclinical or early atherosclerosis in epidemiological and interventional studies. However, there is little knowledge on the relationships between inflammatory biomarkers and CIMT in OSAS. Recently, YKL–40 has been shown to be associated with the presence and severity of OSAS.[7] To the best of our knowledge, there is no information about the relationship between serum YKL–40 level and CIMT in patients with OSAS. Therefore, the aim of the present study was to evaluate serum YKL–40 levels in patients with OSAS and to investigate the possible relationship between serum YKL–40 level and subclinical atherosclerosis, as assessed by CIMT, in OSAS patients.

METHODS

We enrolled 40 consecutive patients newly diagnosed with OSAS by polysomnography and 40 age-sex- and body mass index-matched controls. Exclusion criteria included the following: chronic obstructive pulmonary disease, hypertension (blood pressure ≥140/90 or receiving medications), diabetes mellitus, congestive heart failure, a history of coronary artery disease, cerebrovascular disease, carotid artery stenosis greater than 50%, use of antihypertensive, antidiabetic and lipid-lowering agents, alcohol abuse, renal or liver failure, thyroid disorders, malignancy, a history of psychiatric disorders, any chronic inflammatory disease, and systemic infections at the time of the study or within two weeks before the study. The study protocol was approved by our local ethics committee, and all patients provided written informed consent to participate in the study.

Abbreviations:

AHI	*Apnea-hypopnea index*
CAD	*Coronary artery disease*
CCA	*Common carotid artery*
CIMT	*Carotid intima-media thickness*
IL	*Interleukin*
OSAS	*Obstructive sleep apnea syndrome*
PRTS	*Percentage of recording time spent*
SaO_2	*Oxygen saturation*
TNF	*Tumor necrosis factor*
VSMCs	*Vascular smooth muscle cells*

Polysomnography

All-night attended comprehensive diagnostic sleep studies were performed at the sleep laboratory in our hospital. Polysomnographic monitoring was performed using the standard technique. Apnea was defined as a total cessation of airflow for ≥10 sec, and hypopnea was defined as a reduction in airflow of 50% from baseline for at least 10 sec, a 3% drop in oxygen saturation from the preceding stable saturation, and/or arousal. Apnea-hypopnea index (AHI) was defined as the total number of apneas and hypopneas per hour of sleep. The percentage of recording time spent (PRTS) of oxygen saturation (SaO_2) <90% was calculated as a measure of hypoxemia duration. The diagnosis of OSAS was based on AHI >5 events/h, which was further subdivided into mild (5≤ AHI <15 events/h), moderate (15≤ AHI <30 events/h), and severe (AHI ≥30 -events/h).[8]

Assessment of carotid intima-media thickness

CIMT was measured using the Toshiba Diagnostic Ultrasound System machine (Aplio 500 SSA–780A) with a 7.5–MHz transducer with the patients lying in the supine position. The technique used was in accordance with the consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force.[9] Briefly, CIMT was defined as the distance between the leading edge of the lumen-intima interface and the media-adventitia interface on the far wall of common carotid artery (CCA) (posterior wall). After examination of the transverse and longitudinal planes of the carotid arteries, CIMT was measured in both arteries approximately 1 cm proximal to the carotid artery bifurcation in an area free of

plaque. At least, three measurements were performed on both sides, and averaged. The average of measurements obtained from both CCAs was taken as CIMT.

Analysis of blood samples

After overnight fasting for 12 h, venous blood samples were obtained for all patients from the antecubital space. After clotting, the samples were immediately centrifuged and stored at –20 °C until analysis. HsCRP and the other biochemical parameters were determined by the standard laboratory. The measurement of plasma YKL–40 levels was performed in duplicate with the use of commercially available enzyme-linked immunosorbent assay (ELISA) kits (Cusabio Biotech., Wuhan, China). According to the YKL–40 ELISA kits, the detection range of YKL–40 levels is 46.875–3000 pg/mL.

Statistical analysis

Continuous variables were shown as means±standard deviations or medians (interquartile range) and categorical data were presented as percentages. The one-sample Kolmogorov-Smirnov test was used to evaluate whether the distribution of continuous variables was normal. The continuous variables between 2 groups were compared with Student t test or Mann-Whitney U test. The categorical variables were compared appropriately with chi-square or Fisher exact test. The correlations between variables were tested by the Pearson correlation test for normally distributed variables and with Spearman correlation tests for non-normally distributed variables. Multiple linear regression analysis was used to explore the independent determinants of CIMT. A 2-sided p value <0.05 was considered significant in all analyses. Data were analyzed using SPSS 15.0 version (SPSS Inc, Chicago, Illinois).

RESULTS

The study population consisted of 40 OSAS patients (mean age 50.2±7.6 years; 75% male) and 40 controls (mean age 51.7±8.3 years; 82.5% male). The clinical and laboratory characteristics of OSAS patients and the control subjects are presented in Table 1. The age, sex and BMI distributions did not differ significantly between the groups. In addition, there was no difference between the groups in terms of systolic blood pressure, diastolic blood pressure, fasting blood glucose, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatinine levels and smoking status (all values of p>0.05). The patients with OSAS had significantly increased CIMT compared to those of the controls (0.76±0.16 *vs*. 0.67±0.17 mm, p=0.019). When the laboratory findings were compared, the OSAS group had signifi-

Table 1. Clinical and laboratory characteristics of the study population

	Patients with OSAS (n=40)	Controls (n=40)	*p*
Age, years	50.2±7.6	51.7±8.3	0.405
Sex, male (%)	75	82.5	0.412
Smoking (%)	42.5	45	0.822
Body mass index (kg/m^2)	29.2±3.3	28.6±3.7	0.485
Systolic blood pressure (mmHg)	129 (120–135)	130 (115–135)	0.965
Diastolic blood pressure (mmHg)	80 (70–85)	70 (65–80)	0.265
Fasting blood glucose (mg/dL)	82.8±12.3	80.6±13.8	0.460
Creatinine (mg/dL)	0.81±0.2	0.87±0.2	0.324
Triglycerides (mg/dL)	132.1±35.1	134.8±39.1	0.751
Low-density lipoprotein cholesterol (mg/dL)	128.4±17.9	127.6±24.1	0.879
High-density lipoprotein cholesterol (mg/dL)	36.6±7.9	36±6.7	0.717
Carotid intima-media thickness (mm)	0.76±0.16	0.67±0.17	0.019
High sensitivity C-reactive protein (mg/L)	1.3±0.5	1.0±0.3	0.010
YKL–40 (pg/ml)	161.3±62.4	118.9±81.3	0.011

cantly higher YKL–40 and hsCRP levels (161.3±62.4 *vs*. 118.9±81.3 pg/mL, p=0.011, 1.3±0.5 *vs*. 1.0±0.3 mg/L, p=0.010, respectively) compared to the control group.

Among the 40 OSAS patients, 18 had mild OSAS, and 22 had moderate to severe OSAS. Serum levels of YKL–40 and hsCRP in the patients with moderate to severe OSA (197.6±56.2 pg/mL and 1.4±0.6 mg/L respectively) were significantly elevated compared with the patients with mild OSAS (117±35.4 pg/mL, p<0.001; Figure 1 and 1.1±0.3 mg/L, p=0.031 respectively). Moreover, serum YKL–40 levels were strongly correlated with AHI (r =0.617, p<0.001), and weakly correlated with SaO_2 <90% of PRTS (r=0.394, p=0.012) and hsCRP (r=0.486, p=0.001). CIMT was significantly elevated in the patients with moderate to severe OSAS compared to the patients with mild OSAS (0.81±0.1 *vs*. 0.70±0.1, p=0.037 respectively; Figure 2). In addition, CIMT was strongly correlated with serum YKL–40 levels (r=0.694, p<0.001; Figure 3), hsCRP (r=0.622, p<0.001; Figure 4), age (r=0.525, p=0.001), and weakly correlated with AHI (r=0.365, p=0.021) and SaO_2 <90% of PRTS (r=0.328, p=0.039). To obtain potential determinants of CIMT, the serum levels of YKL–40 and hsCRP, age, AHI, and SaO_2

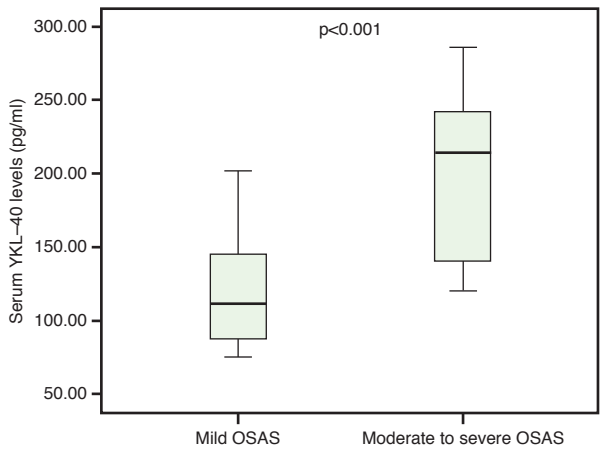

Figure 1. Serum YKL–40 levels in the patients with both mild OSAS and moderate to severe OSAS. OSAS: Obstructive sleep apnea syndrome.

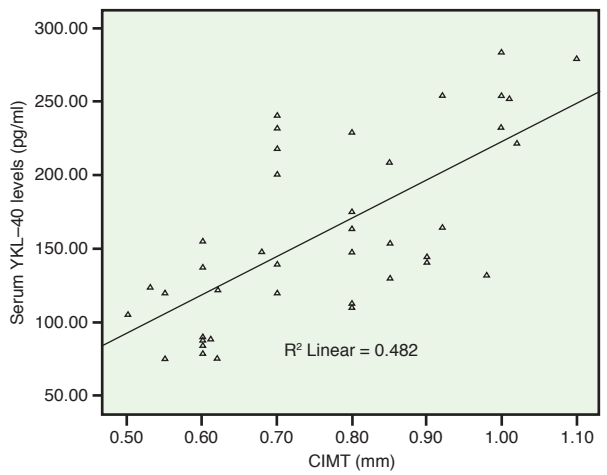

Figure 3. The correlation between carotid intima media thickness and serum YKL–40 levels (r=-0.694, p<0.001).

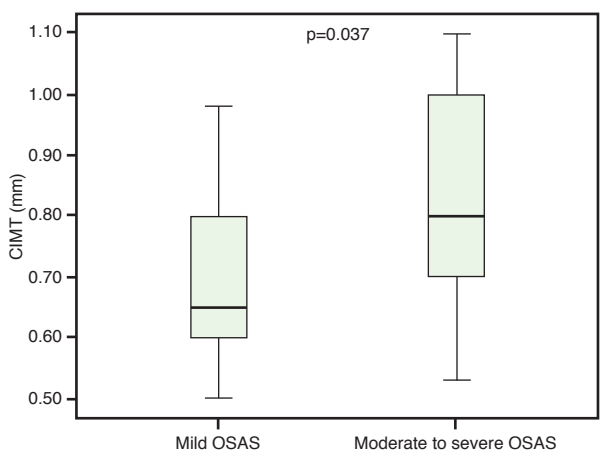

Figure 2. CIMT values in the patients with both mild OSAS and moderate to severe OSAS. CIMT: Carotid intima media thickness; OSAS: Obstructive sleep apnea syndrome.

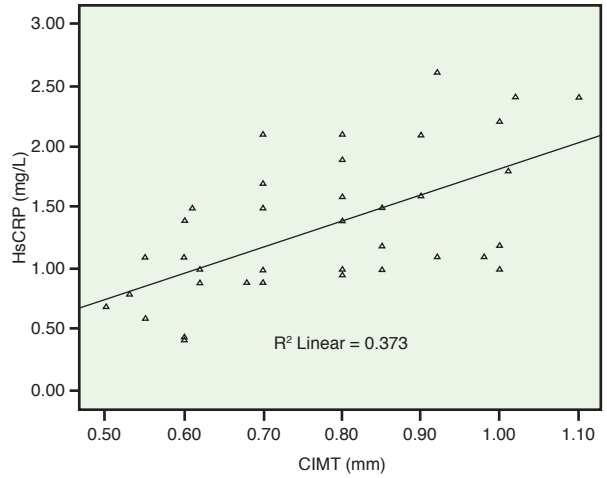

Figure 4. The correlation between carotid intima media thickness and hsCRP levels (r=0.622, p<0.001). HsCRP, high sensitivity C-reactive protein.

Table 2. Model 1, Independent predictors of carotid intima-media thickness

	B	Std.error	Beta	t value	*p*
Constant	0.172	0.123	–	1.395	0.172
Age	0.006	0.003	0.300	2.428	0.020
Apnea-hypopnea index	0.000	0.002	-0.023	-0.154	0.879
<%90, PRTS	0.001	0.001	0.122	1.047	0.302
YKL–40	0.001	0.000	0.570	3.683	0.001

<%90, PRTS: Percentage of recording time spent of oxygen saturation <90%.

Table 3. Model 2, Independent predictors of carotid intima-media thickness

	B	Std.error	Beta	t value	*p*
Constant	0.209	0.143	–	1.454	0.155
Age	0.007	0.003	0.320	2.151	0.038
Apnea-hypopnea index	0.002	0.002	0.174	1.201	0.238
<%90, PRTS	0.001	0.001	0.125	0.974	0.337
hsCRP	0.100	0.047	0.348	2.112	0.042

<%90, PRTS: Percentage of recording time spent of oxygen saturation <90%; hsCRP: High sensitivity C-reactive protein.

<90% of PRTS were used as independent variables in multiple regression analysis. Because YKL–40 and hsCRP are both inflammatory markers, they were not entered together in the regression model. Thus, two regression models including serum levels of YKL–40 and hsCRP were separately consisted (Tables 2 and 3). In these, age and serum levels of YKL–40 and hsCRP were found to be significant predictors of CIMT in the multiple regression analysis.

DISCUSSION

The main points of this study can be summarized as follows: (1) The patients with OSAS had significantly greater CIMT values and higher serum levels of YKL–40 and hsCRP than the control group. (2) CIMT positively correlated with serum levels of YKL–40 and hsCRP, age, AHI and SaO_2 <90% of PRTS, and predictors of increased CIMT were age and serum levels of YKL–40 and hsCRP in the OSAS group. (3) There was a positive relationship between YKL–40 and AHI and SaO_2 <90% of PRTS.

The diagnosis and evaluation of atherosclerosis development at subclinical phase in patients with OSAS is important in terms of risk factor modification, preventing complications due to the related pathology, and risk classification. In this context, ultrasonographic measurement of CIMT is a cheap, reliable and repeatable method used in the evaluation of subclinical atherosclerosis. CIMT is both closely related to conventional cardiovascular risk factors and also predicts future cardiovascular events such as myocardial infarction and stroke.[10] In accordance with results of previous studies, we found that OSAS was related to increased CIMT.[11–13] The intermittent hypoxia observed in the patients with sleep apnea leads to the onset of systemic inflammation, characterized by increased levels of several inflammatory markers.[14] Ongoing inflammatory responses play an important role in atherosclerosis.[15]

YKL–40 is a new inflammatory marker with respect to acute and chronic inflammation as well as cancer. It is expressed and secreted by macrophages, neutrophils, fibroblast-like synovial cells, chondrocytes and VSMCs.[4] It is well known that elevated YKL–40 levels are detected in diseases characterized with inflammation, extracellular remodeling and ongoing fibrosis such as rheumatoid arthritis, infections, type II diabetes and inflammatory bowel disease.[16] Recently, Wang et al.[7] and Li et al.[17] found high serum YKL–40 levels in patients with OSAS, and independently associated YKL–40 levels with the

presence and severity of OSAS. Similarly, the present study demonstrated that serum levels of YKL–40 were significantly higher in the patients with OSAS than in the control subjects, and were associated with the severity of OSAS. Several studies demonstrate that elevated serum YKL–40 levels are independently associated with the presence and extent of CAD and even higher YKL–40 levels are documented in patients with myocardial infarction.[18] Sui et al.[19] reported that serum YKL–40 levels were significantly higher in OSAS patients with CAD compared to those without CAD. It was shown that YKL–40 was especially secreted by macrophages infiltrated in atherosclerotic lesion depths, and the highest YKL–40 expression was observed in the early stages of atherosclerotic lesion development. Moreover, in vitro studies have shown that YKL–40 promotes the attachment, spread and migration of VSMCs.[16] Therefore, YKL–40 is involved in at least two key events in the development of atherosclerosis as well as plaque generation. Furthermore, the participation of YKL–40 in the pathogenesis of vascular incidents and inflammation suggests that this marker may have a role in the development of endothelial dysfunction. Indeed, Jafari et al.[20] demostrated that increased YKL–40 levels in patients with OSAS were associated with hypertension and endothelial dysfunction. It is a well-known fact that endothelial dysfunction is the earliest event in atherosclerosis, and plays a pivotal role in all phases of the atherosclerotic process.[21] Thus, YKL–40 may indirectly contribute to atherosclerosis development. Although it has been shown that serum levels of inflammatory markers, such as interleukin (IL)–6, and tumor necrosis factor (TNF)-α, hsCRP, and IL-18 are significantly associated with CIMT, a well-established marker of subclinical atherosclerosis, the relation between YKL–40 and CIMT levels has not been studied previously in patients with OSAS. In the present study, we demonstrated for the first time that serum levels of YKL–40 are independently associated with CIMT. Thus, the results suggest that increased levels of YKL–40 may play an important role in the progression of atherosclerosis in patients with OSAS.

OSAS is a multicomponent disease including intermittent hypoxia, respiratory efforts, and sleep fragmentation. Intermittent hypoxia and reperfusion during repetitive episodes of nocturnal apnea are probably a source of oxidative stress with production of reactive oxygen species. Oxidative damage plays an important role in the pathogenesis of atherosclerosis and cardiovascular diseases.[22] Akyuz A et al.[23] reported the presence of a correlation between increased CIMT and AHI and SaO_2 <90% of PRTS in patients with OSAS. In another study, increased CIMT was found to be associated with the duration of OSAS-related hypoxia.[13] Similarly, in this study, we found that CIMT was correlated positively with AHI and SaO_2 <90% of PRTS. Furthermore, we found that AHI and SaO_2 <90% of PRTS were significantly correlated with serum levels of YKL–40 and hsCRP in the patients with OSAS. Thus, OSAS-related hypoxia may be indirectly contribute to atherosclerosis progression.

There are several limitations to the present study. Firstly, this was a cross-sectional study with a relatively small number of patients with OSAS. Therefore, the present findings need to be validated in larger prospective studies. Secondly, if we had studied the other inflammatory mediators, such as IL–1, IL–6, TNF-α and IL–8, our findings could have been validated further. Thirdly, the effect of continuous positive airway pressure treatment, which may might have provided further evidence of a link between OSAS, inflammation, and atherosclerosis, was not investigated.

In conclusion, CIMT is significantly correlated with serum levels of YKL–40 and hsCRP, age, AHI and SaO_2 <90% of PRTS. In addition, age and serum levels of YKL–40 and hsCRP are independent predictors of CIMT in patients with normotensive and nondiabetic OSAS. We suggest that the inflammatory responses and hypoxia related to OSAS may be associated with the development of atherosclerosis.

Funding sources

This study is supported by Erzincan University Committee for Scientific Research Projects (EUBAP No: SAG-A-070114-0050).

Conflict-of-interest issues regarding the authorship or article: None declared

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Keywords: Carotid intima-media thickness; coronary artery disease; inflammation; sleep apnea, obstructive; YKL-40.

Anahtar sözcükler: Karotis intima-media kalınlığı; koroner arter hastalığı; inflamasyon; uyku apne, obstrüktif; YKL-40.