Evaluation of the Epicardial Fat Tissue Thickness and Serum Omentin Levels in Patients with Cardiac Syndrome X

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ABSTRACT

Introduction: The aim of this study was to evaluate the correlation between the epicardial fat tissue thickness (EFTT) and serum omentin levels in patients with cardiac syndrome X (CSX).

Patients and Methods: A total of 51 patients with CSX admitted to our clinic were included in the patient group, and 46 healthy subjects were included in the control group. Demographics, routine laboratory tests, and high sensitive C-reactive protein (hsCRP) levels of all patients were recorded. The EFTT was measured with transthoracic echocardiography (TTE). Serum omentin levels were measured with the enzyme-linked immunosorbent assay.

Results: The EFTT was significantly higher in the CSX group ($p< 0.001$). Serum omentin levels were significantly lower in patients with CSX in comparison with the control group ($p< 0.001$). The median age was significantly higher in the CSX group ($p< 0.001$). The white blood count and hsCRP levels showed no significant difference between the CSX and the control group ($p= 0.46$ and $p= 0.49$, respectively).

Conclusion: In our study, we found increased epicardial fat tissue (EFT) thickness and decreased serum omentin levels in patients with CSX, a finding similar with the literature. Thus, increased EFT thickness may play a role in the pathophysiology of CSX by causing a decrease in the serum omentin level.

Key Words: Epicardial fat tissue; omentin; cardiac syndrome X

Kardiyak Sendrom X'li Hastalarda Epikardiyal Yağ Dokusu Kalınlığının ve Serum Omentin Seviyelerinin Değerlendirilmesi

ÖZET

Giriş: Bu çalışmanın amacı kardiyak sendrom X'li hastalarda epikardiyal yağ dokusu ile serum omentin seviyeleri arasındanki ilişkiyi değerlendirmektir.

Hastalar ve Yöntem: Kliniğimizde tanısı konan 51 kardiyak sendrom X hastası, hasta grubuna ve 46 sağlıklı olgu ise kontrol grubuna dahil edilmiştir. Demografik veriler, rutin labarotuvar testleri hsCRP seviyeleri çalışıldı. Epikardiyal yağ dokusu kalınlığı transtorasik ekokardiyografi ile serum omentin seviyeleri ise ELISA yontemi ile ölçüldü.

Bulgular: Epikardiyal yağ dokusu kalınlığı hasta grubunda anlamlı olarak daha kalındı ($p< 0.001$). Kontrol grubu ile karşılaştırıldığında, serum omentin seviyeleri hasta grubunda anlamlı olarak daha düşüktü ($p< 0.001$). Kardiyak sendrom X'li hastalarda medyan yaş anlamlı olarak daha yüksekti ($p< 0.001$). Lökosit sayımı ve hsCRP seviyleri iki grup arasından anlamlı farklılık göstermedi (sırasıyla; $p= 0.46$, $p= 0.49$)

Sonuç: Güncel literatüre benzer şekilde, yapmış olduğumuz çalışmamızda, kardiyak sendrom X'li hastalarda epikardiyal yağ dokusu kalınlığının artmış ve serum omentin seviyelerinin düşük olduğunu gösterdik. Bu bulgular ışığında artmış epikardiyal yağ dokusu, serum omentin seviyelerindeki düşüşe neden olarak koroner sendrom X hastalığının patolojisinde rol oynayabilir.

Anahtar Kelimeler: Epikardiyal yağ dokusu; omentin; kardiyak sendrom X

INTRODUCTION

Coronary arteries are observed to be normal in approximately 30% of patients presenting with typical chest pain and positive cardiac stress test results[(1)]. This condition in which normal epicardial coronary arteries are observed in spite of the existence of myocardial ischemia was defined as cardiac syndrome X (CSX) in 1973 by Kemp et al.[(2)]. Although it is assumed that multiple factors play a role in the CSX pathophysiology, microvascular

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ischemia caused by endothelial dysfunction is the most acknowledged abnormality[3]. In 20%-30% of patients with CSX, symptoms worsen, and the quality of life deteriorates[4]. Furthermore, the mortality rate from myocardial infraction is 1.2%, and a recurrent unstable anginal attack rate is 8.4% in patients with non-ST-elevated acute coronary syndrome and normal coronary arteries[5].

Covering more than three-fourths of the heart, the epicardial fat tissue (EFT) is a specific type of visceral adipose tissue, located between myocardium and visceral pericardium[4,6]. That EFT is an active tissue secreting several mediators such as adipokinin was demonstrated in previous studies[6,7]. The EFT has been assumed to be a cardiovascular diseases risk factor as it secrets several pro-inflammatory cytokines under the effect of paracrine[8,9]. Although the EFT can be measured with transthoracic echocardiography (TTE), computerized tomography (CT), and magnetic resonance imaging (MRI), TTE is considered to be an inexpensive, easier-to-apply, and more reliable method than the others[6].

Nowadays, the adipose tissue has been declared as not only a storage of triglycerides and source for free fatty acids, but also as an endocrine organ that takes part in many metabolic procedures as it secrets several mediators by means of the mature adipocytes it embodies[10]. Omentin, also called intelectin, is a new adipokinin discovered in 2005[11]. Taking charge in the insulin-mediated glucose transportation in human adipocytes, omentin is secreted more from the visceral fat tissue than from the subcutaneous fat tissue[12]. It has been demonstrated that the omentin mRNA is predominantly expressed in human epicardial and omental adipose tissues than in the subcutaneous and the internal mammary artery periadventitial adipose tissue reserves. Omentin, like other periadventitial epicardial adipokines, may also play an important role in the pathogenesis of cardiovascular diseases[11]. It has been demonstrated that omentin increases vasodilatation through nitric oxide (NO), yet it decreases migration, angiogenesis, and vascular inflammation by reducing the release of the tumor necrosis factor-alfa (TNF-α) from endothelial cells[11,13]. Omentin-1 levels are decreased in obese individuals, and there is an inverse ratio between body mass index (BMI) and the omentin level[12]. Serum omentin levels are also found to be lower in obesity-related conditions such as insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, and polycystic ovarian syndrome[13].

In accordance with the information provided above, the present study aims to investigate the relationship between the EFT thickness and serum omentin levels in patients with CSX and with microvascular dysfunction as the most common pathophysiology, as well as to compare their results with the normal population.

PATIENTS and METHODS

Study Design

Approved by the Ethic Committee of İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital, the present study was designed as an observational, cross-sectional study. All participants were informed about the study objectives in advance and signed a letter of consent in accordance with the Helsinki Declaration standards.

Study Population

Fifty-one consecutive patients (16 men, 35 women) diagnosed with CSX in our clinic between January and July 2014 were included in our study. CSX refers to patients with typical chest pain, an evidence of ischemia in the myocardial perfusion scintigraphy, and a normal epicardial coronary lumenogram in coronary angiography. The preliminary diagnosis of vasospastic angina was ruled out in CSX patients, by performing the hyperventilation test following the coronary angiography. The control group was composed of 46 volunteers (17 men, 29 women) admitted to the clinic with atypical chest pain and with negative treadmill test results during the same period as the patient group. Individuals with diabetes mellitus, renal dysfunction (creatinine level > 1.5 mg/dL or GFR < 60 mL/min), acute coronary syndrome, stable coronary artery disease, heart failure, inflammatory or autoimmune disease, chronic obstructive lung disease or any other respiratory problems, and malignancy, and patients who refused to participate in the study were excluded.

Demographic information of both the patient and the control group was registered. Hypertension was defined as the blood pressure ≥ 140/90 mmHg, or the use of anti-hypertensives, while hyperlipidemia was defined as the use of a hypolipidemics, low-density lipoprotein cholesterol (LDL) ≥ 160 mg/dL, total cholesterol > 220 mg/dL, or triglycerides (TG) ≥ 150 mg/dL[14,15]. Finally, BMI was calculated as the body weight divided by the body height squared.

Biochemical Analysis

Venous blood samples were collected from the antecubital vein followed by an overnight fasting. The blood samples were centrifuged at 2000 g (10 min) to remove the serum. Aliquots of serum samples were stored at -80°C until the analysis. Serum glucose, urea, creatinine, LDL, TG, and other biochemical parameters were measured by the Beckman Coulter AU 5800 system with commercial kits (Beckman CoulterInc, USA). Serum hsCRP levels were measured by nephelometry using a BN II nephelometer (Siemens Healthcare Diagnostics, USA). A complete blood count was determined in a Coulter LH 750 auto analyzer (BeckmanCoulter, CA, USA).

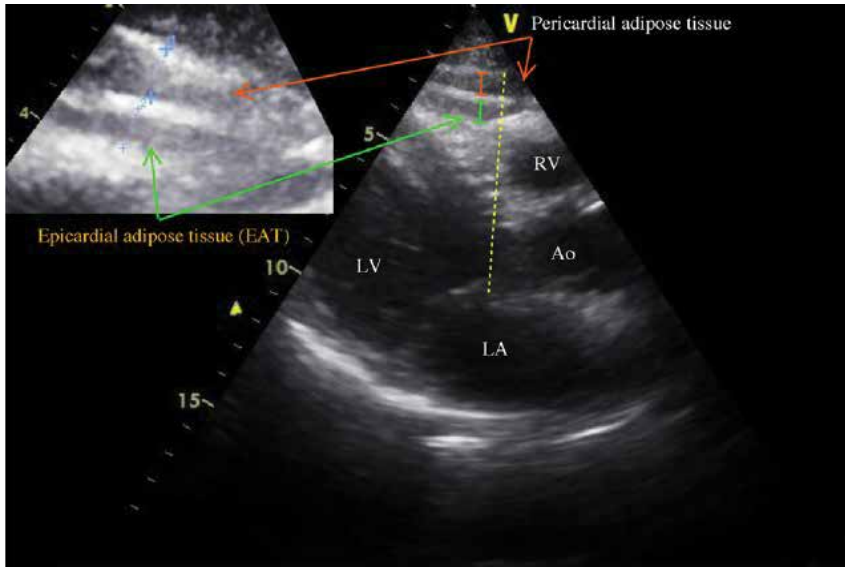

Figure 1. Measurement of epicardial fat tissue (EFT, EAT) thickness by echocardiography. LV: Left ventricle, LA: Left atrium; RV: Right ventricle, Ao: Aorta.

Serum human intelectin-1 (TLN1, omentin) levels were determined by using the human intelectin-1 (TLN1, Omentin) assay enzyme-linked immunosorbent assay kit, according to the manufacturer's instructions (YH Biosearch Laboratory Systems; China; cat. No.: YHB166 Hu). Intra-assay and inter-assay coefficients of variation were < 10% and < 12%, respectively. The omentin level was expressed as ng/L.

Measurement of the Epicardial Fat Tissue

All EFTT were measured after coronary angiography (CAG) by the same cardiology specialist who was blinded to the patients, using a Philips iE33 ultrasound machine with a S5-1 transducer (1-5 MHz) according to standard techniques in accordance with the American Society of Echocardiography recommendations[16]. Aortic annulus was accepted as a reference point for the measurement of EFTT from the parasternal short and long-axis view of the free wall of the right ventricle (Figure 1). The average measurements for both short- and long-axis views were calculated.

Coronary Angiography

Standard selective coronary angiography was performed in all patients showing ischemia evidence on the myocardial perfusion scintigraphy with a Philips Allura Xper FD10 X-Ray system. Coronary angiography was applied to all patients using right femoral catheterization with the Judkins technique, and the results were evaluated by a cardiologist blinded to study. The control group was not evaluated with CAG.

Statistical Analysis

For the comparison of numerical variables between the CSX and control group, Student's t-test was used in case of normal distribution of the variables, while the Mann-Whitney U-test was employed in case of a non-normal distribution. Numerical variables were determined as the median value ± standard deviation, and categorical variables were determined as the ratio (%). Categorical variables of the groups were compared using a chi-squared test or by Fisher's exact test, when necessary. Furthermore, in a correlation analysis, the Pearson test was used for the relation between numerical variables with normal distribution, whereas Spearman's Rho test was used for the relation between numerical variables with non-normal distribution. As for the significant correlation results, the strength and the direction of the correlation were defined by the Rho value. The diagnostic power of EFTT and serum omentin levels showing a significant difference between the CSX patients and the control group were demonstrated by means of the ROC analysis and the ROC curve with the area under curve values. Moreover, a p-value < 0.05 was accepted as statistically significant. Finally, the SPSS 16.0 software (SPSS Inc., Chicago, Illinois, USA) was used for all statistical analyses.

RESULTS

As it was mentioned before, the CSX group was composed of 51 patients (16 men, 35 women), while the control group was composed of 46 volunteers (17 men, 29 women). The median age in the CSX group (56 ± 8.7 years) was significantly higher in comparison to the control group (49.5 ± 9.3 years; p< 0.001). Yet, hyperlipidemia was found to be significantly higher in the control group (p= 0.029). There was no statistically significant difference observed in BMI between the CSX and the control groups (29.4 ± 4.8 and 28.5 ± 6.1, respectively; p= 0.54). Other characteristics

Table 1. Comparison of clinical features of cardiac syndrome X and control groups

	Cardiac syndrome X group (%)	Control group (%)	p
Number of cases	51	46	
Age (median ± SD) (year)	56 ± 8.7	49.5 ± 9.3	< 0.001*
BMI (median ± SD)	29.4 ± 4.8	28.5 ± 6.1	0.54*
Gender			0.56
Male	16 (31.4)	17 (37)	
Female	35 (68.6)	29 (63)	
HT			0.24
(–)	26 (51)	18 (39.1)	
(+)	25 (49)	28 (60.9)	
Smoking			0.09
(–)	10 (19.6)	16 (34.8)	
(+)	41 (80.4)	30 (65.2)	
Family anamnesis			0.94
(–)	17 (33.3)	15 (32.6)	
(+)	34 (66.7)	31 (67.4)	
HPL			0.029
(–)	19 (37.3)	8 (17.4)	
(+)	32 (62.7)	38 (82.6)	
EFTT (mm) (median ± SD)	4.1 ± 0.9	2.8 ± 0.8	< 0.001*

Chi-squared test, *Student's t-test SD: Standard deviation, HT: Hypertension, HPL: Hyperlipidemia, BMI: Body mass index, EFTT: Epicardial fat tissue thickness.

and the comparison between the CSX and the control groups are illustrated in Table 1.

There was no statistically significant difference observed in renal function tests, white blood cells, hemoglobin, and platelet levels between the CSX patients and the control group (Table 2). Also, hsCRP levels were similar between the CSX patients and the control group (2.1 ± 4.8, 1.6 ± 3, respectively; p= 0.49). However, TG levels were significantly higher in the control group (184 ± 77.6 mg/dL) in comparison to the CSX group (132 ± 69.3 mg/dL; p= 0.045).

The EFTT in the CSX group was significantly higher than in the control group (4.1 ± 0.9 and 2.8 ± 0.8 mm, respectively; p< 0.001) (Table 1, Figure 2). Still, the serum omentin levels in patients with CSX were significantly lower than those in the control group (361.9 ± 201.6 and 372.9 ± 191.5 ng/L, respectively; p< 0.001) (Table 2, Figure 3).

The correlation analysis illustrated a weak but significant negative correlation between BMI and omentin; a weak but significant positive correlation between BMI and EFTT; and finally, a moderately significant positive correlation between EFTT and age (Table 3).

Finally, the diagnostic power of EFTT for CSX was observed to be higher than omentin levels in the ROC analysis (Figure 4).

DISCUSSION

The levels of omentin, a newly defined adipokine, were observed to be lower in CSX patients in our study. In accordance with the literature, we found out that EFTT is higher in CSX patients and that there is a weak but significant negative correlation between BMI and serum omentin levels. That the diagnostic power of EFTT is higher than serum omentin levels may indicate that several mediators secreted from the EFT may take part in the development of pathophysiology of the disease.

Even though the etiopathogenesis of CSX is not clear, endothelial dysfunction, inflammation, and abnormal pain sensation are perceived to be the most effective factors[17]. The study by Egashira et al. in 1993 showed that endothelium-dependent dilatation of coronary arteries was impaired in patients with CSX[18]. Furthermore, Quyyumi et al. concluded that the endothelial dysfunction can contribute to a decreased coronary reserve during stress or pain[19]. Microvascular dysfunction (MVD), also known as microvascular angina, can be displayed in a significant proportion of CSX patients by using several objective methods[20,21]. A study by Murthy et al. (2014), illustrated that patients having MVD had higher rates of clinical endpoints such as cardiac death or hospitalization due to heart failure and non-fatal myocardial infraction[22].

Table 2. Comparison of clinical features of cardiac syndrome X and control groups

	Cardiac syndrome X group (%)	Control group (%)	p
hsCRP (mg/dL)	2.1 ± 4.8	1.6 ± 3.7	0.49*
Urea (mg/dL)	29 ± 7.2	26.5 ± 8.5	0.56
Creatinine (mg/dL)	0.7 ± 0.15	0.69 ± 0.15	0.46
LDL (mg/dL)	129 ± 32.9	127 ± 161	0.89*
Total cholesterol (mg/dL)	195 ± 43.4	209 ± 34.4	0.46
HDL (mg/dL)	48 ± 11	47.5 ± 9.8	0.83
Triglyceride (mg/dL)	132 ± 69.3	184 ± 77.6	0.045
HbA1C (%)	5.4 ± 0.37	5.4 ± 0.4	0.56
Omentin (ng/L)	361.9 ± 201.6	372.9 ± 191.5	0.042*
WBC	7000 ± 1380	7070 ± 1470	0.46
Hb (g/dL)	13.1 ± 1.6	13.3 ± 1.4	0.97
PLT	261.000 ± 55.900	267.000 ± 52.800	0.71
Neutrophil count	3700 ± 950	3800 ± 1000	0.28
Lymphocyte count	2060 ± 580	2000 ± 640	0.86

Student's t-test, *Mann-Whitney U-test, SD: Standard deviation.

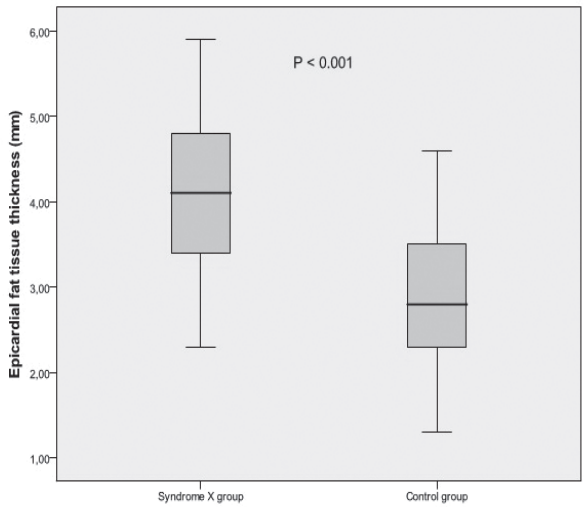

Figure 2. Distribution of epicardial fat tissue thickness in syndrome X and control groups control groups (box-plot).

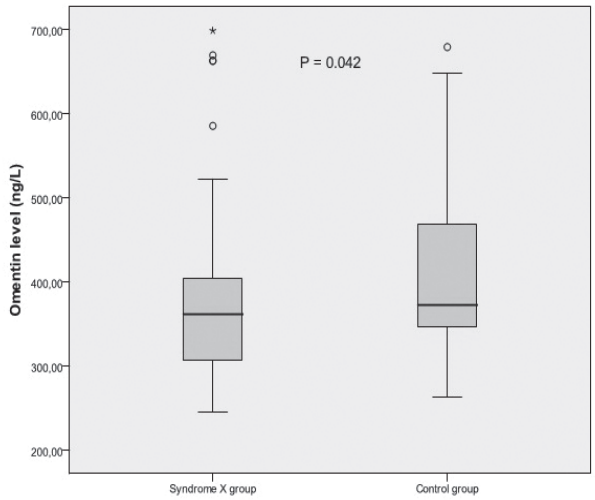

Figure 3. Distribution of serum omentin levels in syndrome X and control groups (box-plot).

EFT is an intrathoracic component of the visceral adipose tissue, located especially in the interventricular and atrioventricular sulcus, the lateral wall of the right ventricle, and around coronary arteries[23]. Even though the EFT thickness can be measured by various methods (CT, MRI), echocardiography is usually the primary choice as it is inexpensive, easily accessible, has no radiation disadvantage, and has correlated results with MRI[23]. By secreting adipokines and cytokines, EFT creates paracrine and vasocrine effects on the heart[24]. EFT can have anti-inflammatory and anti-atherogenic effects by secreting adiponectin and adrenomedullin, but it can also increase the risk of cardiovascular disease with monocyte chemotactic protein (MCP)-1, interleukin (IL)-1β, IL-6, and tumor necrosis factor-alfa TNF-α[24,9]. Sade et al. (2009) found a significantly higher EFTT, C-reactive protein (CRP), and insulin resistance, and a decreased adiponectin level in patients with CSX, that is, women with MVD[25]. The study by Benedicte et al. examining healthy volunteers showed that increased EFTT is associated with decreased coronary microvascular response and that EFT can affect the endothelial function in the early period[26]. Moreover, the studies by Gedikli et al. and Mohammd et al. showed an increased EFTT in patients with CSX[4,6].

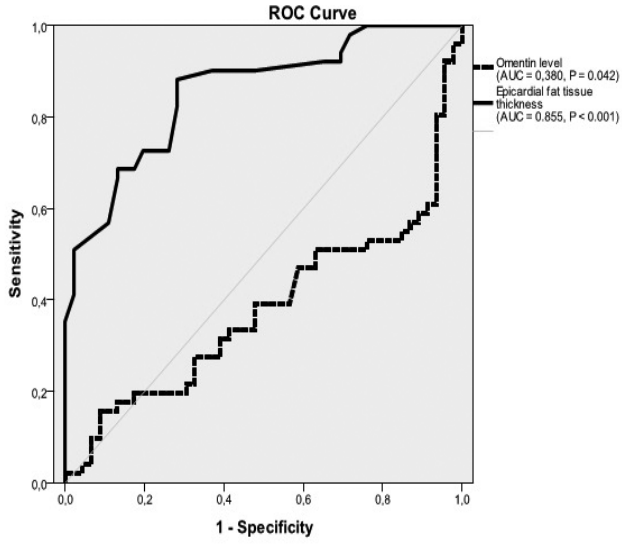

Figure 4. ROC curves of omentin levels and epicardial fat tissue thickness for prediction of syndrome X.

Table 3. Summary of significant correlation results between the serum omentin level, epicardial fat tissue thickness, and other variables

Variables	Rho	p
Omentin-BMI	-0.221	0.03
EFTT-Age	0.482	< 0.001*
EFTT-BMI	0.291	0.004*

Spearman's Rho test, * Pearson's test. BMI: Body mass index, EFTT: Epicardial fat tissue thickness.

Discovered in 2005, omentin is a new adipokine taking part in insulin-dependent glucose transport in human visceral adipocytes[11]. The serum omentin level is observed to be inversely proportional to obesity, insulin resistance, and BMI, but directly proportional to the HDL and plasma adiponectin levels[12]. A study showed that after applying omentin treatment to rat aorta, noradrenaline-dependent vasoconstriction decreased. This result indicates that omentin contributes to vasodilatation through endothelium-derived NO[11]. Moreno et al. demonstrated that serum omentin levels are associated with age, BMI, the waist-to-hip ratio, systolic and diastolic blood pressure, endothelium-dependent vasodilatation, and the IL-6 and CRP levels[27]. The same study showed that omentin can be used as an indicator of endothelial function[27]. Yamawakive et al. found that omentin has anti-inflammatory effects since it regulates the TNF-α-induced cyclooxygenase-2 secretion in vascular endothelial cells[28]. Zhong et al. (2011) detected decreased serum omentin levels in patients with coronary artery disease, as well as a negative correlation between serum omentin levels and BMI and IL-6 levels[29]. Accordingly, it can be concluded that omentin reduces endothelial dysfunction, serves as an anti-inflammatory molecule, and has protective effects in cardiovascular diseases[11].

The relation between the visceral adipose tissue thickness and cardiometabolic diseases, especially the role of various molecules secreted from adipocytes, has been examined via various clinical research. In the light of these studies, parallel to the increased visceral adipose tissue thickness, adipokine levels secreted from adipocytes protective against cardiovascular disease decrease, and precipitating molecule levels increase. In our study, we also found that the CSX patients have increased EFT thickness and decreased omentin levels. We have not directly investigated the relation between the EFT thickness and serum omentin levels, but we may conclude that serum omentin levels may have a negative correlation with the EFT thickness.

Study Limitations

The number of patients and the control group included in the study was the most important limiting factor. Another limiting factor is that the control group did not consist of age- and sex-matched healthy volunteers, because due to our study design, we had to include patients with atypical chest pain and a negative treadmill test. Also, the inability to show microvascular dysfunction in patients with CSX objectively, the measurement of EFTT by transthoracic echocardiography, not studying any inflammatory markers other than hsCRP, and not analyzing the insulin resistance are considered to be other restrictive factors. However, as is stated in the introduction and the discussion sections, the EFTT measurement by echocardiography is not considered to be a major limitation as it is inexpensive, easily accessible, and has correlated results with MRI [6,23].

CONCLUSION

In our study, increased EFT thickness and decreased serum omentin levels are found to be associated with CSX. A higher diagnostic value of EFTT than the diagnostic value of serum omentin levels indicates that the visceral adipose tissue is a pool and affects the development of the disease by secreting various molecules. Our study needs to be supported by additional extensive research in this direction. In addition, to the best of our knowledge, our study is the first to analyze both EFTT and serum omentin levels in patients with CSX.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: İU, EO, AK
Analysis/Interpretation: AŞ, MŞ, Eİ, AK
Data Acquisition: VK, MŞ
Writting: İU, AŞ, EO
Critical Revision: AK, Eİ
Final Approval: All of authors.

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