The serum pentraxin-3 is elevated in patients with cardiac syndrome X

Kardiyak sendrom X'li hastalarda serum pentraksin-3 düzeyi artmıştır

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ABSTRACT

Objectives: Cardiac syndrome X (CSX) is a clinical entity that is defined as normal coronary arteries with angina pectoris and objective sins of ischemia. The correlation between CSX and inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) is well established, however an association with pentraxin-3 (PTX-3) has not been examined. The aim of this study was to investigate the association between PTX-3 and CSX.

Study design: A total of 122 patients (58 female, 64 male, mean age 49.6±5.8 years) with suspected of coronary artery disease (CAD) were included in the study. Those with evidence of ischemia (50 patients with positive treadmill tests, 32 patients with positive myocardial perfusion scintography) underwent coronary angiography (82 patients). Patients with a normal angiogram were considered the CSX group (n=41) and patients with coronary lesions were referred to as the CAD group (n=41). Patients without signs of ischemia served as the control group. Serum PTX-3 and hs-CRP levels were measured in all patients.

Results: The CSX group had significantly increased PTX-3 levels relative to the control group (0.46±0.16 *vs.* 0.23±0.09 ng/ml, p<0.001). However there were no differences in levels of PTX-3 and hs-CRP between the CSX and the CAD groups (PTX-3: 0.46±0.16 *vs.* 0.51±0.13 ng/ml, p=0.21; hs-CRP: 1.04±0.45 *vs.* 1.16±0.64 mg/dl, p=0.62). The control group had significantly lower hs-CRP levels (0.73±0.51 mg/dl) when compared to the both CSX and CAD groups (p=0.03 and p=0.002, respectively). Serum PTX-3 levels were weakly correlated with hs-CRP levels (r=0.30, p=0.001).

Conclusion: PTX-3, a novel inflammatory marker, is elevated in patients with CSX, similar to the well known inflammatory marker hs-CRP, and may be a promising biomarker reflecting inflammatory status in these patients.

ÖZET

Amaç: Kardiyak sendrom X (KSX), anjina pektoris ve objektif iskemi bulgularına rağmen normal koroner arterlerin saptandığı bir tablodur. KSX ile enflamatuvar belirteçler özellikle de yüksek duyarlıklı C-reaktif protein (hs-CRP) arasındaki ilişki iyi bilinmekte olup pentraksin-3 (PTX-3) ile ilişkisi gösterilmemiştir. Bu çalışmada, PTX-3 ile KSX arasındaki ilişki araştırıldı.

Çalışma planı: Çalışmaya koroner arter hastalığı (KAH) şüphesi olan toplam 122 hasta (58 kadın, 64 erkek, ortalama yaş 49.6±5.8 yıl) alındı. İskemi bulgusu (efor testi pozitif 50 hasta, miyokart perfüzyon sintigrafisi pozitif 32 hasta) olan hastalara (toplam 82) koroner anjiyografi yapıldı. Normal koroner anjiyografisi olan hastalar (n=41) KSX grubu ve koroner lezyonu olan hastalar (n=41) KAH grubu olarak kabul edildi. İskemi bulgusu olmayan hastalar kontrol grubuna alındı. Her üç grupta PTX-3 ve hs-CRP düzeyleri araştırıldı.

Bulgular: Kardiyak sendrom X grubunda PTX-3 değerleri kontrol grubuna göre yüksek bulundu (0.46±0.16 ve 0.23±0.09 ng/ml, p<0.001). Ancak KSX grubu ile KAH grubu arasında serum PTX-3 ile hs-CRP düzeyleri yönünden anlamlı fark bulunmadı (PTX-3: 0.46±0.16 ve 0.51±0.13 ng/ml, p=0.21; hs-CRP: 1.04±0.45 ve 1.16±0.64 mg/dl, p=0.62). Kontrol grubunda hs-CRP düzeyi (0.73±0.51 mg/dl), KSX (1.04±0.45 mg/dl) ve KAH (1.16±0.64) grubuna göre anlamlı bir şekilde düşük bulundu (sırasıyla, p=0.03 ve p=0.002). PTX-3 ile hs-CRP arasında pozitif bağıntı olduğu gözlendi (r=0.30, p=0.001).

Sonuç: Pentraksin-3 yeni bir enflamatuvar belirteç olup, KSX'li hastalarda iyi bilinen enflamatuvar belirteçlerden olan hs-CRP gibi yükselmektedir. PTX-3, KSX'li hastalarda enflamatuvar durumu yansıtan bir biyobelirteç olabilir.

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Cardiac syndrome X (CSX) is defined as typical chest pain, objective signs of ischemia, and normal coronary arteries in coronary angiogram.[1] CSX is an important clinical entity which constitutes about 10-20% patients who undergo coronary angiography.[2] The exact pathophysiological mechanism of CSX remains obscure, however coronary microcircular abnormalities and endothelial dysfunction have been proposed as potential mechanisms in the etiology of the disease.[3-5] The association between endothelial dysfunction and inflammation has been well established, and inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP), intercellular cell adhesion molecule-1, and vascular cell adhesion molecule-1 contribute to the pathophysiology of CSX.[6] Moreover, serum hs-CRP is correlated with symptoms and electrocardiographic markers of myocardial ischemia in patients with CSX.[7]

Pentraxin-3 (PTX-3), a newly identified acute phase reactant which resembles CRP structurally and functionally,[8] is produced by many different kinds of cells including macrophages, dendritic cells, neutrophils, fibroblasts, and vascular endothelial cells.[9] Serum PTX-3 levels are elevated in patients with vasculitis,[10] acute myocardial infarction,[11,12] systemic inflammation or sepsis,[13] psoriasis, unstable angina pectoris, and heart failure.[14-18]

The association between CSX and inflammation and inflammatory markers such as hsCRP is well known, however the pathophysiological role of PTX-3 has not been well established in patients with CSX.[19] Therefore, the aim of the present study is to assess the association between PTX-3 and CSX.

PATIENTS AND METHODS

A total of 122 patients were recruited for this study during a six months period. Eighty two stable angina pectoris (SAP) patients with evidence of ischemia (50 patients with positive treadmill test, 32 patients with positive myocardial perfusion scintography) underwent coronary angiography for suspected coronary artery disease (CAD), and 40 age- and sex- matched outpatient subjects with anginal symptoms and a negative treadmill or myocardial perfusion scan test were included as the control group. Patients with typical chest pain, objective ischemia evidence, and normal coronary angiograms were assigned to the CSX group. Forty one patients were assigned to the CSX group and 41 age- and sex- matched SAP patients with coronary lesions were evaluated as CAD group. Coronary artery stenosis was considered significant in the presence of a luminal diameter narrowing of >50% in any of major coronary arteries or their primary branches. The number of significantly stenosed coronary arteries was recorded (one, two, or three vessels respectively). In order to exclude coronary artery spasm, the patients were asked to breathe rapidly and deeply for five minutes during the coronary angiography procedure. Subjects were excluded if coronary spasm, defined as focal or diffuse narrowing in the coronary arteries, was induced during the hyperventilation test. Patients with acute coronary syndrome, history of previous myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention, secondary hypertension (HT), renal failure, hepatic failure, chronic obstructive lung disease and/or manifest heart disease, such as cardiac failure (left ventricular ejection fraction <50%), atrial fibrillation, and moderate to severe cardiac valve disease were excluded from the study. Similarly, patients with infection, acute stress, chronic systemic inflammatory disease, and those who had been receiving medications affecting the number of leukocytes were also excluded. All the participants included in the study were informed about the study, and oral and written consent to participate voluntarily was obtained.

Abbreviations:

BMI	*Body mass index*
CSX	*Cardiac syndrome X*
CAD	*Coronary artery disease*
EIA	*Enzyme immunoassay*
hs-CRP	*High-sensitivity C-reactive protein*
HT	*Hypertension*
PTX-3	*Pentraxin-3*
SAP	*Stable angina pectoris*

Fasting blood samples were collected on the day of coronary angiography for the evaluation of serum parameters. Serum PTX-3 level was measured by enzyme immunoassay (EIA) using a quantitative kit (Human PTX-3/TSG-14 Immunoassay, DPTX30, R&D Systems, Inc, MN, USA). For PTX-3, intra-assay and inter-assay coefficients of variation (CV) ranged from 3.8% to 4.4% and 4.1% to 6.1%, respectively (minimum detectable concentration: 0.025 ng/ml). Hs-CRP was measured in the serum by EIA (Immage hs-CRP EIA kit, Beckman Coulter Inc., USA).

Transthoracic echocardiography was performed and the biplane Simpson's ejection fraction (%) was calculated before coronary angiography. HT was defined as having at least two blood pressure measure-

ments >140/90 mmHg or using antihypertensive drugs, whereas diabetes mellitus was defined as having at least two fasting blood sugar measurements >126 mg/dl or using anti-diabetic drugs. Body mass index (BMI) values were calculated based on the height and weight of each patient. Medications used prior to the coronary angiography were recorded. This study was approved by the local ethics committee.

Statistical analyses

Statistical analyses were conducted using the SPSS 17 (SPSS Inc, Chicago, IL, USA) software package. Continuous variables were expressed as mean±standard deviation or median±interquartile range (IQR), whereas categorical variables were presented as percentages. The differences between normally distributed numeric variables were evaluated by Student's t-test or one way ANOVA, while non-normally distributed variables were analyzed by Mann-Whitney U-test or Kruskal-Wallis variance analysis as appropriate. The chi-square test was employed for the comparison of categorical variables. Correlation analyses were completed using the Pearson test. A p value <0.05 was accepted as significant.

RESULTS

Baseline characteristics

In total, 122 patients (49.6±6.3 years, 53% male) were included in the study. Patients were categorized

Table 1. Baseline clinical and laboratory characteristics of patient groups

Variables	Control group (n=40)			CSX group (n=41)			CAD group (n=41)			*p*
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	
Age (years)			48.7±6.9			49.8±6.6			50.3±5.2	0.66
Sex, male (%)	19	47.5		22	53.7		23	56.1		0.73
BMI (kg/m^2)			24.2±2.3			25.5±3.4			23.5±4.4	0.55
Diabetes (%)	10	25		11	26.8		12	29.3		0.91
Hypertension (%)	17	42.5		20	48.8		21	51.2		0.72
Smoking (%)	18	45		21	51.2		20	48.9		0.44
Ejection fraction (%)			64±4.3			63±2.4			61.2±2.1	0.24
Number of diseased vessel (1/2/3)			NA			NA			18/16/7	
Medications (%)										
Aspirin	18	45		20	48.8		22	53.6		0.72
ACE-I or ARB	20	50		23	56.1		22	53.7		0.34
Beta-blocker	5	13		4	9.8		6	14.6		0.08
CCB	3	7.5		3	7.3		2	4.9		0.84
Statin	7	17.5		9	21.9		9	21.9		0.65
Glucose (mg/dL)			108.1±26.8			124.9±58.0			121.0±46.9	0.86
HDL-C (mg/dL)			39.5±13.3			34.6±8.8			34.6±9.5	0.22
LDL-C (mg/dL)			113.7±34.1			112.9±29.9			117.0±30.9	0.85
Triglyceride (mg/dL)			151.8±61.2			174.1±103.7			158.1±96.3	0.74
BUN (mg/dL)			13.2±3.9			16.5±6.2			18.0±10.2	0.08
Creatinine (mg/dL)			0. 78±0.18			0.87±0.39			0.88±0.28	0.26
hs-CRP (mg/dL)			0.73±0.51			1.04±0.45			1.16±0.64	**<0.001**
PTX-3 (ng/mL)			0.23±0.09			0.46±0.16			0.51±0.13	**<0.001**

CSX: Cardiac syndrome X; CAD: Coronary artery disease; BMI: Body mass index; ACE-I: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CCB: Calcium channel blocker; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; BUN: Blood urea nitrogen; hs-CRP: High sensitivity C-reactive protein; PTX-3: Pentraxin-3.

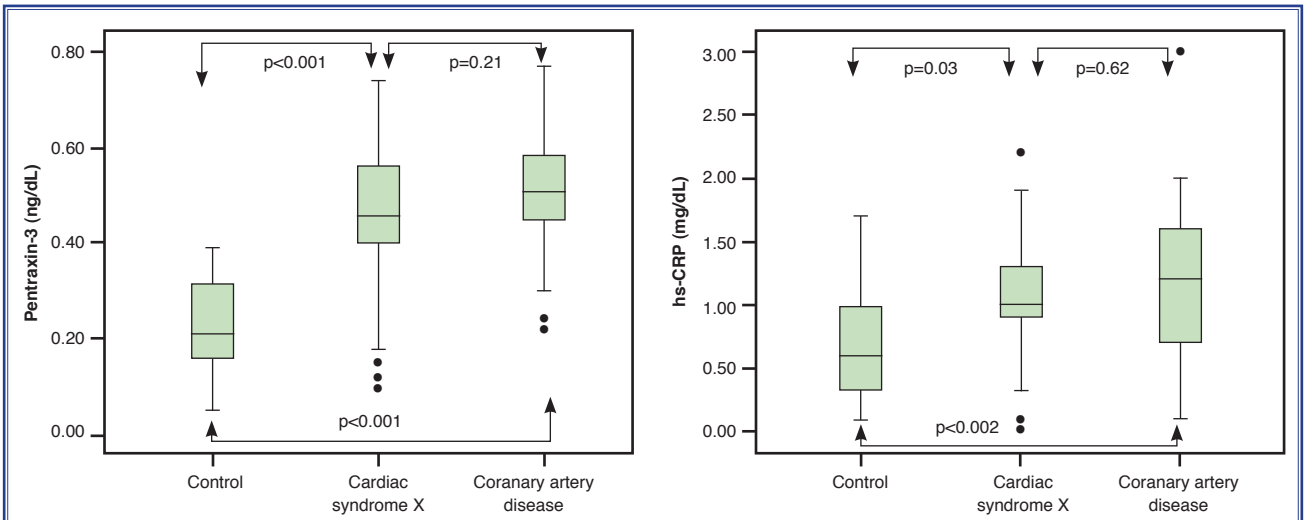

Figure 1. Pentraxin-3 and hs-CRP levels of patients according to groups. hs-CRP: High-sensitivity C-reactive protein.

into three groups as the control group (n=40), CSX group (n=41), and CAD group (n=41). Baseline clinical, angiographic and laboratory characteristics of the patients groups are shown in Table 1. Age, sex, HT, diabetes, BMI and medication use were not different between the groups.

The serum levels of hs-CRP and PTX-3 are shown in Figure 1 for each group. Significantly increased PTX-3 levels were observed in the CSX group relative to the control group (0.46±0.16 *vs.* 0.23±0.09 ng/mL, p<0.001). However there were no difference in the levels of PTX-3 between the CSX and the CAD groups (0.46±0.16 *vs.* 0.51±0.13 ng/mL, p=0.21). Similarly, there were no differences in hs-CRP between the CSX and CAD groups (1.04±0.45 *vs.* 1.16±0.64 mg/dl, p=0.62). The control group had significantly lower hs-CRP levels (0.73±0.51 ng/dl) when compared to the both CSX (p=0.03), and CAD groups (p=0.002). Univariate correlation analysis revealed a positive correlation between serum PTX-3 levels and hs-CRP levels (r=0.30, p=0.001; Figure 2).

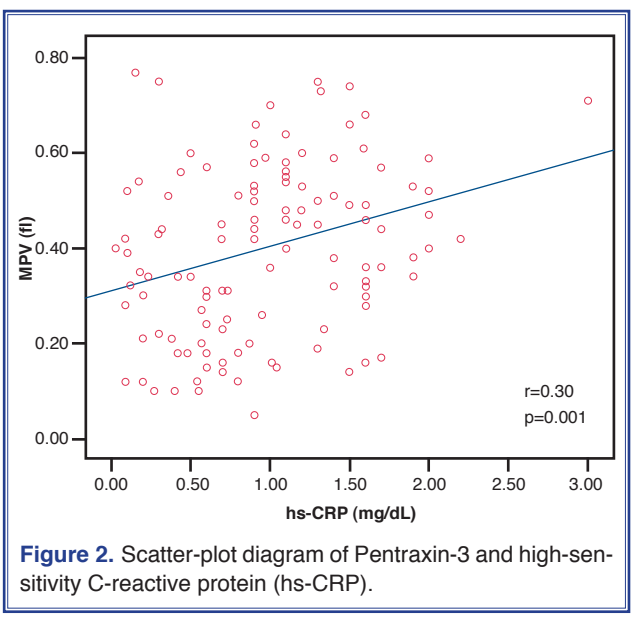

Figure 2. Scatter-plot diagram of Pentraxin-3 and high-sensitivity C-reactive protein (hs-CRP).

DISCUSSION

In this study, we investigated the association between the serum PTX-3 and CSX. In patients with CSX, the levels PTX-3, a newly identified inflammatory marker, were increased relative to the control group and similar to the CAD group. PTX-3 levels were correlated with hs-CRP levels in patients with CSX, consistent with the established association between CSX and other serum markers of inflammation.

Pentraxin-3, produced by various cell types including macrophages, dendritic cells, neutrophils, fibroblasts, and vascular endothelial cells,[9] is essentially an acute phase reactant that is functionally and structurally similar to CRP.[8] PTX-3 is secreted after an inflammatory stimulus and may reflect the local inflammatory status in tissues.[20,21] Serum PTX-3 levels are elevated in many conditions including acute myocardial infarction,[11,12] unstable angina pectoris and heart failure,[14-17] systemic inflammation or sepsis,[13] psoriasis[13] and vasculitis.[10] Higher PTX3 levels

were reported to be associated with adverse cardiovascular outcomes in acute coronary syndromes[12,22] and stable coronary disease, independent of systemic inflammation.[19] However, to our knowledge, this is the first report demonstrating the association of PTX-3 levels with CSX.

Endothelial dysfunction and impaired coronary microcirculation are two main entities that have been proposed to be responsible for CSX.[3-5] Indeed, impaired coronary microcirculation is closely related to endothelial dysfunction. The association of inflammatory markers with endothelial dysfunction has been well established. Vane et al.[5] have shown that inflammatory cytokines and growth factors may produce an inflammatory and proliferative response in the vessel wall that may in turn cause microvascular impairment. In other studies, hs-CRP was correlated with angina and profound impairment of endothelial vascular reactivity as well as biomarkers of endothelial dysfunction.[5,23,24] In the present study, we found that hs-CRP and PTX-3 were increased in both the CSX and CAD groups relative to the control group. These findings were consistent with the literature regarding the role of inflammation in CSX. We propose that although coronary angiograms revealed normal epicardial coronary arteries in the CSX group, both CSX and CAD groups have similarly increased inflammatory status. It was previously reported that the leukocytes found in the coronary artery lumen are primarily neutrophils.[25] PTX-3 is stored in specific granules of neutrophils and released in response to inflammatory signals.[26] Therefore serum PTX-3 levels may be a more sensitive marker of the inflammatory state in the coronary artery compared to serum hs-CRP. However, the exact role of PTX-3 in the pathophysiology of atherosclerosis is not fully understood. In previous studies, PTX-3 was found to be produced in areas of atherosclerosis, and the production of PTX-3 may contribute to pathogenesis of this disease.[25] It has been suggested that PTX-3 may be part of a protective mechanism, inducing vascular repair by inhibiting fibroblast growth factor-2 or other growth factors responsible for smooth muscle proliferation.[27,28] However, the pathophysiological role of PTX-3 still remains controversial.

Limitations

The major limitation of the present study is the low number of patients included. Data regarding additional inflammatory markers such as IL-6 and TNF-α, would give a more detailed picture of the inflammatory state in these patients. The CAD group included in our study had stable angina. This group was relatively low risk group when compared to a high-risk disease state such as unstable angina. Therefore, our CAD group reflected only the inflammatory state of stable coronary disease, which may be considered a limitation. Because there was no long-term follow up of these patients, our study provides no prognostic data in terms of future cardiovascular events. In order to rule out coronary artery spasm, a hyperventilation test was performed. Although hyperventilation is a safe provocative test, it is less sensitive in detecting coronary spasm when compared with ergonovine injection, a potential limitation of our study design limitation.

Pentraxin-3, a novel inflammatory marker, is elevated in patients with CSX, similar to the well known inflammatory marker hs-CRP, and may be a promising biomarker in reflecting the inflammatory state of patients with CSX.

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

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Key words: Angina pectoris/etiology; cardiac syndrome X; C-reactive protein; coronary angiography; coronary artery disease; PTX3 protein; syndrome.

Anahtar sözcükler: Anjina pektoris/etyoloji; kardiyak sendrom X; C-reaktif protein; koroner anjiyografi; koroner arter hastalığı; PTX3 proteini; sendrom.