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Original Article CARDIOLOGY

Serum prolidase activity in patients with cardiac syndrome X

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ABSTRACT

OBJECTIVE: Although the underlying mechanism is not yet fully understood, Cardiac Syndrome X (CSX) is defined as microvascular dysfunction. Prolidase plays a role in collagen synthesis. Increased serum prolidase activity (SPA) has been shown to correlate with collagen turnover. Augmented collagen turn-over may be associated with vascular fibrosis and microvascular dysfunction. In this study, we assessed whether there was a correlation between CXS and prolidase activity.

METHODS: This case-control study included 45 consecutive CSX patients (mean age 50.7±6.5 years, 27 women) and 40 healthy controls (mean age 51.2±6.5 years, 25 women). Prolidase activity was determined with the Human Xaa-Pro Dipeptidase/Prolidase enzyme-linked immunosorbent assay kit (Cusabio Biotech Co. Ltd, China).

RESULTS: Mean prolidase activity was 898.8±639.1 mU/mL in the CSX group and 434.1±289.8 mU/mL in the control group ($p<0.001$). In ROC analysis, it was found that the SPA value above 350 mU/mL sympathizes with the diagnosis of CSX.

CONCLUSION: Increased SPA in CXS patients may play an essential role in the pathophysiology of CSX, leading to augmented oxidative stress and vascular fibrosis, endothelial dysfunction, and increased microvascular resistance.

Keywords: Cardiac syndrome X; collagen; serum prolidase activity.

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Cardiac syndrome X (CSX), also known as microvascular angina, is characterized by the absence of typical exercise angina, ST-segment changes during exercise stress testing, documentation of objective ischemia in myocardial perfusion scintigraphy, or stenosis or vasospasm in epicardial coronary arteries [1]. Coronary microvascular dysfunction and endothelial dysfunction have been proposed as potential mechanisms of the disease. However, the pathophysiological mechanisms in coronary microvascular dysfunction are still unclear [2]. Although it was previously considered as a benign condition, recent studies have shown that CSX is associated with persistent chest pain, a decrease in quality of life, recurrent angiography, and an increase in cardiovascular morbidity and mortality [3].

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Collagen types I and III are determined to be present in high amounts in the tunica intima, media, and adventitia of human coronary arteries. Collagen is the main structural load-bearing element in arterial walls and for that reason, any defects in collagen synthesis or degradation may cause many structural alterations. In healthy individuals, collagen turnover is closely regulated and the proportion of collagen to elastin does not change. However, any imbalance in collagen turnover causes disproportionate storage of ECM protein. Augmented collagen proportion and devastation of the elastin fibers with a proinflammatory microenvironment participate in ECM remodeling, causing increased vascular stiffness due to intima-media thickening [4].

Prolidase (manganese-dependent) is an imino dipeptidase that plays a significant role in collagen biosynthesis, ECM remodeling, and cell maturation. Also, prolidase is responsible for the degradation of dipeptides with C terminal proline and hydroxyproline [5]. Many tissues, such as bone, connective tissue, mucosa of intestine, heart, liver, kidney, brain, uterus, thymus, erythrocytes, leukocytes, fibroblasts, serum, and plasma contain prolidase enzyme. Since it has a large tissue distribution, it is thought that disturbances in prolidase enzyme activity may play a role in the progress of many diseases [6]. In many studies, a relationship between serum prolidase activity (SPA) and the prevalence of coronary artery disease, arrhythmia, and some other cardiovascular diseases, such as hypertension, has been reported [7–9]. Suner et al. [10] have also shown that SPA increases in patients with a slow coronary flow where microvascular dysfunction plays a significant role in the pathogenesis.

As increased extracellular matrix turnover may have a role in the pathophysiology of microvascular dysfunction, we assume that SPA will increase in CSX. This study was planned to estimate the relationship between CSX and SPA.

MATERIALS AND METHODS

This study was approved by the local ethics committee (date: 05.11.2012, no: 2012/15/01).

Study Population

Between June 2010 and June 2012, in Bakirkoy Dr. Sadi Konuk Training and Research Hospital Cardiology clinic, 45 patients having typical exercise angina who were diagnosed with CSX with positive exercise stress electrocardiography (ECG; >0.1 mV ST-segment depression, J point in two or more contiguous leads) or with ischemia in myocardial perfusion scintigraphy and angiographically normal coronary arteries were included in this study. The following criteria were defined as exclusion criteria in the following patient group: heart failure, valvular heart disease, atrial fibrillation, left branch block, myocarditis, slow flow phenomenon, vasospastic angina, hypertension, hyperlipidemia, diabetes mellitus, malignancy, acute or chronic hepatic and/or renal failure, acute or chronic infectious disease or systemic diseases, such as collagen tissue disease. Forty consecutive asymptomatic healthy subjects without any angina or equivalent complaints with a 10-year cardiac event rate of less than 10%, according to the Framingham risk score, were included in the control group [11]. Coronary angiography was not required in control group cases due to the exclusion of ischemia through exercise tests. Demographic features of all study participants, such as age and gender, were recorded and body mass index (BMI), was calculated. Almost all patients underwent transthoracic echocardiography to exclude structural heart disease. All the participants in this study signed the informed consent form. This study was conducted in accordance with the Declaration of Helsinki.

Coronary Angiography

Coronary angiography was performed using the Judkins technique (Siemens Medical Solutions, Erlangen, Germany) via the right femoral artery. The data were assessed by two experienced cardiologists who were blind to the clinical data. Coronary artery disease (CAD) is defined as a stenosis >20% in any of the main coronary arteries, such as intermittent marginal or large diagonal branches. The presence of epicardial coronary artery spasms was checked on coronary angiography with ergonovine administration and/r prolonged hyperventilation.

Laboratory Analysis

All the patients were invited to the clinic weeks after angiography and peripheral venous blood samples were obtained from all participants after eight hours of fasting. The samples were instantly centrifuged (3000 x g for 10 minutes), and the sera were collected. Glucose, triglyceride, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and C-reactive protein (CRP) levels were measured using usual laboratory methods. Sera were frozen at -80°C and stored until the analysis day. SPA was calculated with the Human Xaa-

Table 1. Demographic and biochemical characteristics of the study population

	Control group Mean±SD (min.–max.)		CSX group Mean±SD (min.–max.)		p	
Gender (n, %)						
Female	25	62.5	27	0.6	0.813	X^2
Male	15	37.5	18	0.4		
Age	51.2±6.5 (40–66)		50.7±6.5 (35–60)		0.717	t
BMI	26.84±2.3 (23–31)		27±3.4 (21–32)		0.549	m
Systolic BP (mmHg)	111.4±13.3 (90–135)		117.5±15.2 (90–150)		0.066	m
Diastolic BP (mmHg)	68.4± 9.2 (50–85)		74.2±10.9 (55–95)		**0.02**	m
CRP (mg/L)	0.4±0.4 (0.01–1.7)		0.7±1.2 (0.01–7.17)		0.258	m
Urea (mg/dl)	32.3±8.8 (17–54)		30.2±6.9 (18–49)		0.402	m
Creatinine (mg/dl)	0.8±0.1 (0.54–1.06)		0.7±0.1 (0.54–1.01)		**0.005**	m
Fasting glucose (mg/dl)	91.3±12.7 (65–128)		95.8±12.6 (74–119)		0.1	m
LDL–cholesterol (mg/dl)	108.9±52.2 (39–216)		112±23.8 (60–165)		0.197	m
HDL–cholesterol (mg/dl)	40.2±8 (28–58)		41.8±10,4 (25–74)		0.708	m
Triglycerides (mg/dl)	147.3±54.1 (43–330)		149.4±67 (56–373)		0.746	m
Total–cholesterol (mg/dl)	178.1±52.4 (98–292)		185.6±39.3 (58–270)		0.176	m
SPA (mUml)	434.1±289.8 (115–1200)		898.8±639 (219–3058)		**0.000**	m

BP: Blood pressure; BMI: Body mass index; HDL-cholesterol: high-density lipoprotein cholesterol; CRP: C-reactive protein; LDL-cholesterol: Low-density lipoprotein cholesterol; SD: Standard deviation; SPA: Serum prolidase activity; min: Minimum; max: Maximum; t: t-test; m: Mann-Whitney u test; X^2: Chi-square test.

Pro Dipeptidase/Prolidase Enzyme-linked Immunosorbent Assay kit (Cusabio Biotech Co Ltd, China) according to instructions of the manufacturer.

Statistical Analyses

Among descriptive statistics, mean, standard deviation, median, the lowest and highest values, frequency and ratio were used in the analyses of the data. The distribution of the variables was determined by the Kolmogorov Smirnov test. An analysis of quantitative data, independent sample t-test and Mann-Whitney U test were used. Chi-square test was used in the analysis of qualitative data. The level of effect was investigated by univariate and multivariate logistic regression. The effect level and cut-off value were explored by the ROC curve. SPSS 22.0 program was used for the analyses. The results were evaluated within confidence intervals of 95% and 99% and at a level of statistical signi¬ficance of $p<0.05$ and $p<0.01$.

RESULTS

In this study, the CSX group with 45 (27 female) patients with a mean age of 50.7±6.5 years, and the control group with 40 (25 female) subjects with a mean age of 51.2±6.3 years were included. The demographic characteristics, including age, gender, BMI, Systolic blood pressure (Systolic BP), cholesterol levels, fasting glucose, CRP, and urea concentration, were similar in two groups ($p>0.05$). Diastolic blood pressure (Diastolic BP) was significantly higher in patients with CSX compared with the control group, while the creatinine level was significantly lower ($p<0.05$). The demographic and biochemical measurements of the study participants are summarized in Table 1. SPA was significantly higher in the CSX group than the control group (898.8±639.1 mU/mL, 434.1±289.8 mU/mL, respectively, $p<0.001$, Table 1, Fig. 1). SPA, creatine and diastolic BP were determined to be significantly associated with the CSX in logistic regression analysis. In multivariate logistic regression analysis, SPA and creatine levels were determined to be the independent predictors of CSX presence (Table 2).

In ROC analysis, SPA greater than 350 mU/ml had 81.8% sensitivity and 57.5% specificity (ROC area under curve: 0.69, 95% CI: 0.582–0.812, $p=0.002$) for accurately predicting CSX diagnosis (Fig. 2).

Table 2. Variables associated with the CSX according to univariate and multivariate logistic regression analysis

	Univariate analysis			Multivariate analysis		
	OR	%95 CI	p	OR	%95 CI	p
Serum prolidase activity	1.003	1.001–1.004	**0.000**	1.003	1.001–1.005	**0.002**
Creatine	0.00	0.00–0.17	**0.005**	0.001	0.001–0.045	**0.003**
Diastolic BP	1.06	1.01–1.11	**0.013**			

BP: Blood pressure; CI: Confidence intervals; OR: Odds ratio.

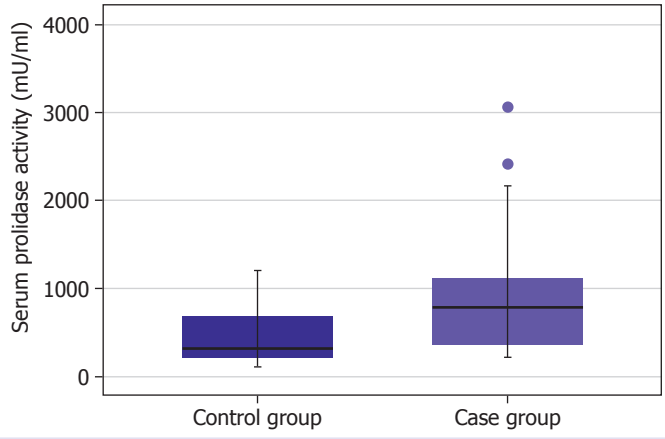

Figure 1. Serum prolidase activity in patients with cardiac syndrome X and control group.

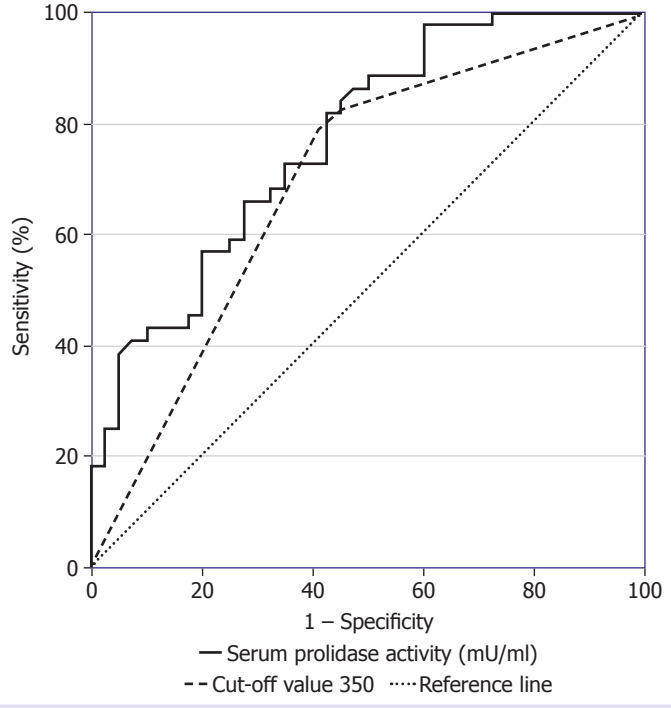

Figure 2. Receiver operating characteristic curve analysis for serum prolidase activity in cardiac syndrome X.

DISCUSSION

Our study showed that SPA increased significantly in patients with CSX and was independently associated with CSX. Cardiac syndrome X is defined as typical angina, positive stress test, and normal epicardial coronary angiogram [1, 12]. In a pathophysiological aspect, the only well-known cause of CSX is microvascular dysfunction, but the underlying pathophysiological mechanisms could not be defined exactly [1].

Despite the non-occluded epicardial coronary artery, these patients have objective findings of myocardial ischemia [12]. Stress myocardial scintigraphy studies revealed reversible myocardial perfusion defection patients with CSX. In the light of these findings, small vessel coronary artery disease, abnormal coronary vascular resistance, and subendocardial ischemia have been suggested as possible mechanisms of microvascular dysfunction; but none of them have been universally accepted as a causal factor [13].

In recent years, coronary vascular fibrosis is suggested to play an important role in the etiology of microvascular dysfunction in CSX. Inflammation, perivascular fibrosis and apoptosis of endothelial cells in small vessels were determined in an analysis of endomyocardial biopsy specimens of CSX patients [14]. Bozcali et al. [15] reported an increase in galectin-3 levels in CSX patients, which is the sign of both vascular fibrosis and inflammation.

In collagen, proline and hydroxyproline comprise 25% of the amino acids. Prolidase is a cytosolic exopeptidase that has an essential role in collagen turnover and matrix remodeling. Prolidase cleave imino dipeptides contain-

ing proline or hydroxyproline on carboxy-terminal. Prolidase enzyme activity has been reported to be a rate-limiting factor in the regulation of collagen biosynthesis [16]. Prolidase activity is regulated by the interaction of ECM proteins, mainly with the interaction of type I collagen and β1-integrin receptor, in normal fibroblasts [5]. Augmented lysosomal enzymes and fibroblast turnover both indicate the increased collagen turnover, which are associated with increased prolidase activity in fibroblasts [17]. In early periods of chronic liver disease, the SPA was shown to increase, demonstrating the presence of liver fibrosis [18]. Similarly, Duong et al. [19] also reported elevated prolidase activity in the keloid tissue. In another study, the SPA was reported to be increased during pulmonary fibrosis in a rat model [20]. When all these studies are evaluated, it can be suggested that increased prolidase activity may be an important marker in fibrotic diseases. Thus, elevated SPA determined in CSX patients in this study may be the underlying cause of microvascular dysfunction by way of vascular fibrosis.

Despite the non-existence of angiographic abnormalities, many patients with CSX have considerable intimal thickening and atheromatous plaques in the coronaries in intra-vascular ultrasonography imaging [21]. Bugiardini et al. [22] reported that in CSX, endothelial dysfunction is a marker of atherosclerosis development. In addition, magnetic resonance imaging revealed abnormal subendocardial perfusion in patients with CSX [23]. The incidence of coronary calcification in CSX (53%) was significantly higher than that of normal controls (20%) in a multi-slice computerized tomography scan [24]. Patients with CSX have been reported to have significantly higher carotid intima-media thickness and augmented arterial stiffness compared to controls. These results point out the early phase or precursor of atherosclerosis [25].

Recently, the effects of cardiac and arterial ECM turnover on plaque rupture and remodeling in atherosclerosis development have been investigated. The levels of matrix metalloproteinases (MMP) and tissue inhibitors of metalloproteinases (TIMP) are important predictors of ECM turnover. The association of CAD with enhanced ECM and collagen turnover has been shown, and this condition may also be related to atherosclerotic plaque instability and remodeling process. Moreover, the associations of TIMP, MMP and subgroup levels have also been shown with carotid vascular diseases, stent thrombosis, acute coronary syndromes, and severity and complexity of the lesion in CAD [26, 27]. In many studies, another indicator of collagen and ECM turnover is reported as the serum prolidase level [28].

Prolidase has been shown to be importantly higher in CAD patients, and prolidase activity has been reported to be associated with CAD severity [7]. Surazynski et al. [16] suggested that prolidase may have an undefined role in angiogenic signaling and that increased prolidase activity is associated with elevated nuclear hypoxia-inducible factor-1 alpha level. Savas et al. [29] have achieved important results in patients with erectile dysfunction, indicating that high SPA is associated with erectile dysfunction. Another study focused on increased serum prolidase levels in mesenteric and peripheral ischemia groups [30].

Another mechanism considered to be involved in CSX pathophysiology is increased oxidative stress. In CSX, microvascular dysfunction is distributed as patchy on the myocardium, and inflammation is mediated by oxidative stress [31, 32]. Oxidative stress directly or indirectly through the reduction of nitrite oxide (NO) bioavailability, which leads to disturbing the endothelium-dependent vasodilatation, it has been involved in the pathophysiology of microvascular angina [33]. Demir et al. [31] reported increases in ischemia-modified albumin concentrations, high-sensitive CRP, and oxidative stress parameters in patients with CSX. Endothelial dysfunction in atherosclerosis has also been associated with augmented oxidative stress that may be significant in the pathogenesis of CSX.

Prolidase activity is defined as an indicator of oxidative stress in many diseases, such as diabetes, diabetic neuropathy, chronic liver diseases, and erectile dysfunction [6, 18, 29, 34]. Hilali et al. [35] determined that increased SPA and oxidative stress may be related to elevated cardiovascular risk in polycystic over syndrome. In addition, Yildiz et al. [7] determined that serum SPA is directly related to oxidative stress and may be used as an oxidative stress indicator.

Tabur et al. [36] determined that SPA levels increased in patients with metabolic syndrome; they also notified there was a negative correlation between SPA and total antioxidant status. Verma et al. [37] have reported that SPA was increased in patients with diabetic nephropathy (DN) and end-stage renal disease concerned with Type 2 Diabetes Mellitus (T2DM) than healthy volunteers. It is emphasized that the increase in SPA causes more oxidative stress burden than healthy volunteers in T2DM and DN patients and may play an important role in the

progression of the disease [37]. Oxidative stress causes collagen degradation, and this process is regulated by prolidase [38]. Moreover, the severity of oxidative stress is directly connected with the inhibition of collagen construction, and prolidase is considered to be the main enzyme of this procedure [39]. In this study, the SPA was studied as the marker of both vascular fibrosis and oxidative stress. In light of all these data, the SPA may be suggested as a predictor in the diagnosis of CSX. To our knowledge, this is the first study in the literature that defines a cut-off value of the SPA in the prediction of CSX.

Elevated SPA may show increased vascular intimal collagen conversion rate and oxidative stress in CSX patients. It may have an essential role in the pathophysiology of CSX, leading to increased oxidative stress and vascular fibrosis, endothelial dysfunction and increased microvascular resistance. Moreover, elevated SPA may also be a factor in the expansion of atherosclerotic plaques in CSX patients, which may be an important marker of cardiovascular events and prognosis in the patient group.

There are some limitations of this study that should be mentioned, such as case-control design, fewer patients and the absence of follow-up data. Due to the lack of long-term follow-up data, any assessment could not be made about the predictive value of SPA in cardiovascular events in CSX patients. Lack of investigation of other oxidative stress markers, such as total antioxidant status, total oxidant status, level of NO, vitamins (C and E), glutathione peroxidase, and glutathione-S-transferase was another limitation. Finally, an objective measurement of microvascular dysfunction was not performed in CSX patients.

In conclusion, our study showed that there was an independent relationship between the increased SPA and CSX. This increase in SPA may cause microvascular dysfunction in CSX patients due to increased collagen turnover, vascular fibrosis, and increased oxidative stress. Furthermore, clinical trials are warranted to clear up the role of SPA in pathophysiological alterations in patients with CSX.

Informed Consent: Informed consent was taken from all participants.

Ethics Committee Approval: This study approved by the Bakirkoy Dr. Sadi Konuk Training and Research Hospital Clinical Studies Ethical Committee (date: 05.11.2012, number: 2012-15-01).

Conflict of Interest: No conflict of interest was declared by the authors.

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Authorship Contributions: Concept – GA, BD; Design – GA, AG, TU, OFB; Supervision – GA, OK, AA, SK, MK; Materials – GA, MK, BD, AG; Data collection and/or processing – GA,TU, AG; Analysis and/or interpretation – GA, AA, OFB; Literature review – GA, AA, OK; Writing – GA, BD, MK; Critical review – GA, BD, MK, SK.

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