

Association between soluble lectin-like oxidized low-density lipoprotein receptor 1 levels and coronary slow flow phenomenon

Ilker Murat Caglar¹, Cem Ozde¹, Ismail Biyik², Fatma Nihan Turhan Caglar³, Ibrahim Faruk Akturk⁴, Murat Ugurlucan⁵, Osman Karakaya¹

¹Department of Cardiology, Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey

²Department of Cardiology, Usak State Hospital, Usak, Turkey

³Department of Cardiology, Istanbul Education and Research Hospital, Istanbul, Turkey

⁴Department of Cardiology, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Turkey

⁵Department of Cardiovascular Surgery, School of Medicine, Istanbul University, Istanbul, Turkey

Corresponding author:

Ismail Biyik, Asc. Prof.
Cardiologist
Department of Cardiology
Usak State Hospital
64100 Uşak, Turkey
Phone: +90 5424173209
E-mail: ismailbiyikmd@yahoo.com

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Abstract

Introduction: The coronary slow flow phenomenon (CSFP) has been associated with myocardial ischemia, myocardial infarction, life-threatening arrhythmias, sudden cardiac death and increased cardiovascular mortality similar to coronary artery disease (CAD). Possible underlying mechanisms of CSFP are endothelial dysfunction, chronic inflammation, microvascular dysfunction and diffuse atherosclerosis. Soluble lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1) seems to play an important role in the pathogenesis of atherosclerosis. We hypothesized that sLOX-1 might be associated with CSFP, and aimed to research the relationship between sLOX-1 and CSFP.

Material and methods: Forty patients with angiographically proven CSFP and 43 patients with a normal coronary flow pattern (NCFP) were included in this study. Coronary blood flow was measured according to the Thrombolysis In Myocardial Infarction (TIMI) frame count method. sLOX-1 levels were measured in all study subjects.

Results: Serum levels of sLOX-1 were significantly higher in the CSFP group than the NCFP group (1061.80 ±422.20 ng/ml vs. 500.043 ±282.97 ng/ml, $p < 0.001$, respectively). Multivariate logistic regression analysis including sLOX-1, MPV, GGT and uric acid levels revealed a significant association between sLOX-1 levels and CSFP (Exp (B)/OR: 1.006, 95% CI: 1.002–1.010, $p = 0.001$).

Conclusions: The present study demonstrated that serum sLOX-1 levels were significantly higher in patients with CSFP and there was a strong association between high sLOX-1 levels and CSFP. High serum sLOX-1 levels may have an important role in the pathogenesis of CSFP. Future studies are needed to confirm these results.

Key words: coronary slow flow phenomenon, soluble lectin-like oxidized low-density lipoprotein receptor 1, coronary slow flow phenomenon.

Introduction

The coronary slow flow phenomenon (CSFP) is an angiographic finding characterized by slow progression of angiographic contrast media in the coronary arteries in the absence of obstructive coronary artery disease (CAD) [1]. The incidence of CSFP ranges between 1% and 7% among patients undergoing coronary angiography [1]. This phenomenon occurs most commonly in young men and smokers and patients admitted with acute coronary syndrome [1, 2]. The clinical course is complicated, with over 80% of patients experiencing recurrent chest pain, most occurring at rest, necessitating readmission to the coronary care unit in almost 20% of affected patients [2]. The CSFP has been associated with myocardial ischemia, myocardial infarction, life-threatening arrhythmias, sudden cardiac death and increased cardiovascular mortality similar to CAD [1–4]. Importantly, “primary” CSFP should be distinguished from “secondary” causes of CSFP. These include angioplasty or stenting for acute myocardial infarction, coronary artery stenosis, coronary artery ectasia, coronary artery spasm, valvular heart disease and connective tissue disorders [1]. The underlying pathophysiological mechanisms of primary CSFP have not been clearly revealed so far. Microvascular dysfunction, endothelial dysfunction, vasomotor dysfunction, small vessel dysfunction, diffuse atherosclerosis, inflammation, oxidative stress and increased platelet aggregability have been evaluated as potential underlying mechanisms so far [1–6]. The oxidative modification of LDL (ox-LDL) has greatly higher proatherogenic and proinflammatory properties than native LDL [7]. Effects of ox-LDL on vascular cells in the development process of atherosclerosis seem to be mediated by its receptors. In this process, ox-LDL becomes a ligand for scavenger receptors such as lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), which is not recognized by the native LDL receptor [8]. The LOX-1 is expressed in all cell types involved in the development of atherosclerotic plaque such as macrophages, endothelial cells and vascular smooth muscle cells and can be stimulated dynamically by ox-LDL, inflammation, shear stress and angiotensin II, which are also risk factors for atherosclerosis [9–12]. The LOX-1 is released as soluble forms after proteolytic cleavage that can be measured in serum, and sLOX-1 serum levels reflect the expression of LOX-1 [13]. Published studies have shown the association between LOX-1 and endothelial dysfunction, inflammation, atherogenesis, acute coronary syndromes, myocardial infarction, obesity, type 2 diabetes mellitus, coronary artery ectasia and coronary lesion complexity in patients with CAD [13–15]. According to our knowledge, there are no

published reports investigating the associations between sLOX-1 and CSFP in the English literature.

In the present study, we hypothesized that sLOX-1 might be associated with CSFP, and aimed to research the relationships between sLOX-1 and CSFP.

Material and methods

Study population

The present observational, case-control comparative study was conducted in a tertiary heart center. Two thousand five hundred fifty consecutive patients undergoing coronary angiography after myocardial ischemia was demonstrated by exercise stress testing or myocardial perfusion scintigraphy were enrolled for the study within a period of approximately 3 years. Two groups were constituted. Forty consecutive patients showing CSFP were selected as the patient group (CSFP group), which consisted of 17 women and 23 men with an average age of 56.33 ± 13.04 years. Forty-three consecutive patients with a normal coronary flow pattern (NCFP) showing normal myocardial blushing and clearing were considered as the control group (NCFP group), which consisted of 27 women and 16 men with an average age of 55.6 ± 6.51 years. A detailed medical history was obtained from all patients and a complete physical examination was performed. The patients were evaluated by means of twelve-lead electrocardiography. A detailed transthoracic echocardiography was performed by two experienced specialists. The diagnosis of hypertension was established by a systolic blood pressure of 140 mm Hg or higher, or a diastolic blood pressure of 90 mm Hg or higher by at least three different measurements, or the use of anti-hypertensive medication. The diagnosis of diabetes mellitus was established by a fasting blood glucose of 126 mg/dl or higher, or the use of anti-diabetic medication. Fasting blood glucose of 100 mg/dl to 126 mg/dl was defined as impaired fasting glucose. Hyperlipidemia was defined as total cholesterol levels of 200 mg/dl or higher, or a history of statin use except in the last 3 months. Patients who were smoking before hospitalization were accepted as smokers. The exclusion criteria of the present study were known CAD, acute coronary syndrome, peripheral arterial disease, congestive heart failure with an ejection fraction < 55%, history of surgical or interventional cardiovascular procedure, stroke, pulmonary hypertension, valvular heart disease, cardiomyopathies, myocarditis, pericarditis, hepatic or renal dysfunction, chronic inflammatory diseases, malignancies, active infections, and endocrine or metabolic disorders except diabetes mellitus. Patients taking antiaggregants, anticoagulants,

corticosteroids, statins in the last 3 months, antioxidant vitamins and alcohol were also excluded from the study.

The study protocol was approved by the local ethics committee and written informed consent was taken from all patients. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines.

Coronary angiography

Coronary angiography was performed using the standard Judkins technique. All angiography procedures were performed by two experienced interventional cardiologists blinded to the clinical characteristics of the patients. We used iohexol as a nonionic contrast agent during coronary angiography in all patients and control subjects. During coronary angiography, the contrast agent was manually injected as approximately 6 to 10 ml at each position. Coronary arteries were visualized in standard planes. Coronary flow rates of all subjects were documented using the Thrombolysis in Myocardial Infarction frame count (TFC) method described by Gibson *et al.* [16]. The TFCs of the left anterior descending (LAD) and circumflex (Cx) arteries were assessed in either the right anterior oblique projection with caudal angulations or the left anterior oblique projection with cranial angulations and that of the right coronary artery (RCA) usually in straight left anterior oblique projection. The initial frame is defined as the frame in which concentrated dye occupies the full width of the proximal coronary artery lumen, touching both borders of the lumen, and forward motion down the artery. The final frame is designated when the leading edge of the contrast column initially arrives at the distal end. The last frames used for the LAD, Cx and RCA were those in which the dye first entered the mustache segment, the distal bifurcation segment, and the first branch of the posterolateral artery, respectively. The final count was then subtracted from the initial count and the exact TFC was calculated for the given artery. The TFC of the LAD artery was corrected by dividing the final count by 1.7. Due to different durations required for normal visualization of coronary arteries, the corrected cutoff values were 36.2 ± 2.6 frames for LAD, 22.2 ± 4.1 frames for Cx, and 20.4 ± 3.0 frames for the RCA, as has been reported previously in the literature [16]. Patients with a TFC greater than two standard deviations from the normal published range for any one of the three vessels were assigned as CSFP. The mean TFC for each patient and control subject was calculated by adding the TFCs for LAD, Cx and RCA and then dividing the obtained value by three. The evaluation of all coronary angiograms and TFC counting

were performed by two other interventional cardiologists blinded to the clinical status and laboratory measurements of the patients.

Blood sampling and biochemical measurements

Blood samples of all individuals were taken from an antecubital vein following an overnight fasting state just after coronary angiography for biochemical analysis. Patients and controls were called again for the measurements of serum sLOX-1 levels. After centrifugation at 3,000 g for 10 min, serum and plasma samples were frozen and stored at -80°C on average for up to 3 months until all samples had been collected from all patients, and the assays were performed as soon as the kits were opened. Serum sLOX-1 levels were determined by a sandwich enzyme-linked immunosorbent assay (ELISA) method using a human sLOX-1 ELISA KIT (Aviscera Bioscience, USA) using two different human sLOX-1-specific antibodies as previously described [17]. The lower limit of detection for sLOX-1 was 0.50 ng/ml. Analyses were performed by the immunologists blinded to the condition of the samples and clinical and angiographic characteristics of the patients. Complete blood count tests were performed by an Automatic Hematology Analyzer (Beckman Coulter, USA) within 1 h after the venous puncture. Fasting blood glucose, total cholesterol, HDL, triglycerides and LDL were measured by an autoanalyzer (Abbott Architect C 16000, USA) using the hexokinase method, the enzymatic method, the accelerator selective detergent method, the glycerol phosphate oxidase method, and the Friedewald formula, respectively. Urea, creatinine, and uric acid levels were also measured by an autoanalyzer (Abbott Architect 16200, USA) using the spectrophotometric method, and hsCRP was measured by an analyzer (Siemens, BN II, Germany) using the nephelometric method. HgA_{1c} levels were studied using a Primus Ultra 2 analyzer (Primus Corporation, Kansas City, Kansas, USA) with the high performance liquid chromatography (HPLC) method.

Statistical analysis

All statistical analyses were performed using SPSS for Windows version 19.0 (SPSS, Chicago, IL, USA). For the descriptive statistics of the data, mean, standard deviation, rate, and frequency values were used. The Kolmogorov-Smirnov test was used to evaluate whether the distribution of continuous variables was normal. For the analysis of parametric data, Student's *t*-test was used. For the analysis of non-parametric data, the Mann-Whitney *U* test was used. The χ^2 test was used to com-

pare the categorical variables between groups. For correlation analysis, Pearson correlation analysis was used. Logistic regression analysis was used to determine the impact of variables. Standardized β coefficients and 95% confidence intervals (CI) were calculated. Statistical significance was defined as $p < 0.05$.

Results

The demographic and clinical characteristics of the patients and controls are shown in Table I. There were no statistically significant differences between the two groups. The laboratory findings of the patients and controls are shown in Table II. The comparisons of TFCs and sLOX-1 levels of the CSFP group and NCFP group are also presented in Table II. Serum sLOX-1 levels were significantly higher in the CSFP group compared to the NCFP group (1061.80 \pm 422.20 pg/ml vs. 500.043 \pm 282.97 pg/ml, $p < 0.001$, respectively, Table II). Serum sLOX-1 levels were not statistically significantly different between diabetic and non-diabetic CSFP patients (1055.23 \pm 388.73 pg/ml vs. 1067.17 \pm 456.77 pg/ml, respectively, $p = 0.930$). The corrected TFC for LAD, Cx, RCA, and the mean TFC were significantly higher in patients with CSFP compared to the NCFP group ($p < 0.001$, Table II). Spearman correlation analysis revealed that there were significant correlations between sLOX-1 levels and TFC-LAD value ($r = 0.678$, $p < 0.001$), TFC-CX value ($r = 0.669$, $p < 0.001$), TFC-RCA value ($r = 0.539$, $p < 0.001$) and TFC mean value ($r =$

0.723, $p < 0.001$), but there was no significant correlation between sLOX-1 levels and hs-CRP values ($r = 0.039$, $p = 0.729$). Mean platelet volume (MPV), γ glutamyl transferase (GGT) and serum uric acid levels were also significantly higher in patients with CSFP (Table II), but multivariate logistic regression analysis including sLOX-1, MPV, GGT and uric acid levels revealed that there was a significant association between sLOX-1 levels and CSFP (Exp (B)/OR: 1.006, 95% CI: 1.002–1.010, $p = 0.001$, Table III).

Discussion

The present study revealed significantly higher soluble lectin-like oxidized low-density lipoprotein receptor 1 levels in patients with the coronary slow flow phenomenon compared to patients with angiographically normal coronary arteries. A strong relationship was demonstrated between sLOX-1 and CSFP measured with corrected TIMI frame counts. According to our knowledge, this is the first report demonstrating the association between coronary slow flow phenomenon and soluble lectin-like oxidized low-density lipoprotein receptor 1 levels. It has been pointed out that CSFP may be a systemic phenomenon rather than limited to coronary arteries and caused by the interplay between local features of coronary arteries and systemic pathophysiological factors [1]. Histopathological examinations showed evidence of small vessel abnormalities such as endothelial thickening due to cell edema, capillary dam-

Table I. Comparisons of demographic and clinical characteristics

Parameter	CSFP group (n = 40)	NCFP group (n = 43)	Value of p
Age [years]	56.33 \pm 13.04	55.6 \pm 6.51	0.749
Gender (male/female)	23/17	16/27	0.064
Diabetes mellitus	18	12	0.105
Hypertension	25	35	0.055
Hyperlipidemia	17	12	0.264
Family history	1	6	0.061
BMI [kg/m ²]	28.708 \pm 5.16	27.967 \pm 3.91	0.392
Systolic BP [mm Hg]	132.29 \pm 12.5	131.78 \pm 13.56	0.722
Diastolic BP [mm Hg]	80.6 \pm 8.5	81.3 \pm 9.7	0.595
Medical therapy:			
β -Blockers	9	10	0.731
CCB	8	9	0.728
ACEI/ARB	9	9	0.943
ASA	8	10	0.791

BMI – Body mass index, BP – blood pressure, ACEI – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor blocker, ASA – acetyl salicylic acid, CCB – calcium channel blockers.

Table II. Comparisons of laboratory findings, TIMI frame counts and sLOX-1 levels

Parameter	CSFP group (mean \pm SD) (median/min-max)	NCFP group (mean \pm SD) (median/min-max)	Value of <i>p</i>
TFC-LAD	43.8 \pm 11.7	17.7 \pm 4.7	< 0.001
TFC-RCA	25.4 \pm 8.4	11.1 \pm 3.1	< 0.001
TFC-Cx	27.9 \pm 6.9	11.9 \pm 4.8	< 0.001
TFC-mean	32.3 \pm 6.4	13.7 \pm 5.0	< 0.001
sLOX-1 [pg/ml]	1062 \pm 422 (1015/324-2508)	500 \pm 283 (411/0-1245)	< 0.001
FBG [mg/dl]	105.22 \pm 24.22	96.60 \pm 14.24	0.050
HbA _{1c} (%)	6.23 \pm 0.428	6.04 \pm 0.489	0.073
Urea [mg/dl]	27.66 \pm 8.27	30.00 \pm 7.0	0.209
Creatinine [mg/dl]	0.79 \pm 0.15	0.73 \pm 0.16	0.171
TG [mg/dl]	191.92 \pm 47.60	187.25 \pm 55.21	0.682
LDL [mg/dl]	129.025 \pm 36.50	121.60 \pm 39.66	0.379
HDL [mg/dl]	41.10 \pm 10.31	41.46 \pm 11.94	0.882
Uric acid [mg/dl]	5.83 \pm 1.42	4.83 \pm 1.04	< 0.001
AST [U/l]	19.7 \pm 6.2	18.2 \pm 3.1	0.329
ALT [U/l]	19.8 \pm 6.3	19.1 \pm 2.8	0.791
GGT [U/l]	31.5 \pm 11	20.3 \pm 5.9	< 0.001
WBC [$\times 10^3$ /ml]	6.4 \pm 1.7	6.3 \pm 1.6	0.949
Hemoglobin [g/dl]	13.02 \pm 1.95	13.35 \pm 0.97	0.330
Platelet [$\times 10^3$ /ml]	229.92 \pm 59.15	239.72 \pm 44.01	0.392
MPV [fl]	8.5 \pm 1.0	7.4 \pm 0.5	< 0.001
LVEF (%)	62.44 \pm 3.32	62.47 \pm 3.36	0.833
hsCRP [mg/l]	1.06 \pm 1.96 (0/0-11)	2.52 \pm 12.27 (1/0-81)	0.588

FBG – Fasting blood glucose, LDL – low-density lipoprotein, HDL – high-density lipoprotein, TG – triglyceride, LVEF – left ventricle ejection fraction, hsCRP – high-sensitivity C-reactive protein, WBC – white blood cells, MPV – mean platelet volume, AST – aspartate transaminase, ALT – alanine transaminase, GGT – γ glutamyl transferase, sLOX-1 – soluble lectin-like oxidized low density lipoprotein receptor-1, TFC – TIMI frame count.

Table III. Results of multivariate logistic regression analysis

Parameter	<i>B</i>	S.E.	Wald	df	Sig. (<i>p</i> value)	Exp(<i>B</i>)	95.0% CI for EXP(<i>B</i>)	
sLOX-1	0.006	0.002	10.914	1	0.001	1.006	1.002	1.010
GGT	0.223	0.081	7.589	1	0.006	1.250	1.066	1.465
MPV	1.556	0.647	5.784	1	0.016	4.738	1.334	16.837
Uric acid	0.227	0.361	0.395	1	0.530	1.255	0.618	2.548
Constant	-23.847	6.385	13.947	1	< 0.001	0.000		

age, and reduced luminal diameter of the small vessels in patients with CSFP [1, 13]. In addition to previously mentioned mechanisms of CSFP, increased homocysteine levels and oxidative stress

parameters have been claimed as other potential underlying mechanisms so far [18, 19]. The LOX-1 is a multiligand receptor, whose ligands consist of oxidized low-density lipoprotein, advanced gly-

cation end-products, platelets, neutrophils, apoptotic or aged cells and bacteria [20]. Sustained expression of LOX-1 by critical target cells including endothelial cells, smooth muscle cells and macrophages sets the stage for chronic cellular activation and tissue damage and contributes to the formation and development of atherosclerotic plaques [20]. The levels of sLOX-1 are increased in inflammatory and atherosclerotic conditions and are related to acute coronary syndrome, severity of CAD, serum biomarkers for oxidative stress and inflammation, which suggests that sLOX-1 may be a useful marker for vascular injury [20]. English *et al.* showed that inhibition of LOX-1 prevents endothelial dysfunction [21]. Kenney *et al.* revealed that microvascular dysfunction correlates with serum LDL and sLOX-1 receptor concentrations [22]. A positive correlation between endothelial dysfunction, microvascular damage and sLOX-1 levels was found by another study [23]. High levels of sLOX-1 play an important role in vascular inflammation, inflammatory diseases and disease activity [24, 25]. Thus, one can infer from these reports that high levels of sLOX-1 are associated with impaired endothelial function, microvascular dysfunction, increased levels of inflammation and atherogenesis, which may explain the relationship between high levels of sLOX-1 and CSFP. So, it may be suggested that LOX-1 may play a role in CSFP. It has also been reported that high sLOX-1 levels may be used to differentiate acute coronary syndrome (ACS) patients from non-ACS patients and to detect plaque rupture in the emergency department [26]. It has been suggested that sLOX-1 might be a useful biomarker of coronary plaque vulnerability in patients with CAD [27]. Li *et al.* reported that postprocedural serum sLOX-1 levels are associated with coronary in-stent restenosis (ISR) in patients with stable CAD and might be useful for the detection and risk assessment of ISR after percutaneous coronary interventions [28]. Lubrano *et al.* suggested that sLOX-1 levels are up-regulated during CAD progression and are associated with inflammatory markers and the measurement of the circulating soluble form of this receptor may be potentially useful in predicting CAD progression [29]. It has been reported that increased serum sLOX-1 levels may reflect enhanced oxidative stresses in vascular walls [30]. Kopetz *et al.* suggested that there was an inflammatory and oxidative stress process in the pathogenesis of the ACS presentation associated with the CSFP [31]. The binding of oxidized low-density lipoprotein to LOX-1 reduces endothelial nitric oxide synthase (eNOS) expression and the intracellular concentration of nitric oxide in endothelial cells through increased production of superoxide and increases in matrix metalloproteinase-1, -3, -9 and collagenase activity [20]. All of the above re-

ports support the association between high levels of sLOX-1 and CSFP.

In the present study, hsCRP levels were not significantly different among patients with and without CSFP. Actually, sLOX-1 may increase in acute phases of ACS, but may not always increase in other acute inflammatory processes in which serum hsCRP levels increase. Kume *et al.* were not able to demonstrate a correlation between serum sLOX-1 levels and hsCRP [12]. The present study revealed that serum sLOX-1 levels were higher in patients with CSFP than NCFP, but no difference was found in hsCRP levels between CSFP and NCFP patients.

Diabetes is a well-known major risk factor of atherosclerosis. It has been reported that LOX-1 expression can be increased by glucose both in macrophages and in endothelial cells [20]. In the present study, serum sLOX-1 levels were not different between the diabetic and non-diabetic CSFP patients, which may be related to strict blood glucose control or the small number of patients with diabetes in this study.

The present study also has some limitations. It was a single center study and limited to the observations of native vessels. The number of patients was small, representing a major limitation. Another limitation of our study is its observational nature.

In conclusion, in the present study, it was demonstrated that serum sLOX-1 levels were significantly higher in patients with CSFP than patients with NCFP and there was a strong association between high sLOX-1 levels and CSFP. High serum sLOX-1 levels may have an important role in the pathogenesis of CSFP. Large scale studies are needed to confirm the results of the present study.

Conflict of interest

The authors declare no conflict of interest.

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