Clin Res Cardiol (2012) 101:247–253
DOI 10.1007/s00392-011-0386-0

ORIGINAL PAPER

Circulating soluble lectin-like oxidized low-density lipoprotein receptor-1 levels are associated with proximal/middle segment of the LAD lesions in patients with stable coronary artery disease

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Received: 6 September 2011 / Accepted: 15 November 2011 / Published online: 25 November 2011

Abstract
Background/Objectives Atherosclerosis is the main underlying pathology of coronary artery disease (CAD), which is the leading cause of mortality worldwide. Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is involved in multiple phases of vascular dysfunction, including endothelial dysfunction, atherosclerotic plaque formation, and destabilization. The purpose of the current study was to determine whether soluble LOX-1 is associated with proximal/mid and distal segment of the left anterior descending (LAD) artery lesion in patients with stable CAD.
Methods Sixty-four patients with proximal/mid segment of the LAD lesions and 51 patients with distal segments of the LAD lesions were included in this study. Soluble LOX-1 levels were measured in all study subjects.
Results Baseline characteristics of the two groups were similar. In stable CAD, patients with proximal/middle segment of the LAD lesions had significantly higher circulating soluble LOX-1 levels than patients with distal segments of the LAD lesions (1.07 ± 0.33 vs. 0.70 ± 0.17 ng/ml, $p < 0.001$). No correlation was found between plasma-soluble LOX-1 levels and fasting glucose, lipid profile. For predicting proximal/middle LAD lesions, the highest specificity (95,2%) and sensitivity (53,8%) levels were obtained at the cut-off value of 0.68.
Conclusion Our study demonstrated that serum-soluble LOX-1 levels were associated with proximal/mid segment of the LAD lesions. Furthermore, this study suggested soluble LOX-1 might be a useful biomarker of coronary plaque vulnerability in patients with stable CAD. Soluble LOX-1, the novel biochemical marker, may provide new insights into not only risk stratification but also therapeutic strategy for CAD.

Keywords Atherosclerotic plaque · Coronary artery disease · Proximal/mid segment of the LAD lesions · Soluble lectin-like oxidized low-density lipoprotein receptor-1

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Introduction

Cardiovascular disease (CVD) [1], including myocardial infarction (MI), unstable angina pectoris, sudden cardiac death and stroke, remains one of the leading causes of morbidity and mortality in the developed world. Atherosclerosis is the main cause of CVD, including ischemic stroke and coronary artery disease (CAD) [2–9]. Advances in recent research have provided greater understanding of the underlying pathophysiology of atherosclerosis and its clinical manifestations. Evidence now supports that atherosclerosis is a progressive, dynamic, and inflammatory process [6, 7, 10]. Atherosclerosis occurs preferentially at certain sites within the arterial tree-at the branching points of a coronary artery [5, 10]. Atherosclerotic lesions of the proximal segment of the left anterior descending (LAD) coronary artery constitute a special subgroup of CAD, given the high-risk profile [11, 12].

Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), a type II membrane glycoprotein and scavenger receptor, is the major receptor for oxidized low-density lipoprotein (ox-LDL) in endothelial cells [13]. It is also expressed by macrophages and vascular smooth muscle cells [14]. LOX-1 has been implicated in vascular inflammation and atherosclerotic plaque formation and

destabilization [15, 16]. LOX-1 is a receptor with an expression that is not constitutive but dynamically inducible [17]. In addition to ox-LDL, LOX-1 can also be activated by other risk factors of CAD, including shear stress, angiotensin II, proinflammatory cytokines, and C-reactive protein [18–21]. Activation of this receptor initiates intracellular signaling pathways leading to endothelial activation, dysfunction and apoptosis, and plaque destabilization [22]. LOX-1 is expressed on the cell surface and can be proteolytically cleaved at its membrane proximal extracellular domain and released as soluble forms (sLOX-1), which can be measured in the serum [23]. Since the level of soluble receptors in circulating blood may reflect the expression of membrane proteins and disease activities, sLOX-1 may be a potential biomarker of vascular disease.

In clinical and pathologic studies, the proximal and mid portions of the major coronary arteries have been identified as the most frequent sites of plaque rupture that have resulted in acute coronary events [24–30]. We therefore sought to clarify the link between circulating sLOX-1 levels and angiographic proximal/mid and distal LAD coronary lesions in stable CAD patients. The present study was the first to evaluate the relationship between sLOX-1 and proximal/mid and distal LAD coronary lesions.

Materials and methods

Patient population

From January 2010 to June 2011, we prospectively evaluated 1,984 patients, for elective coronary angiograms to determine the possible presence of CAD in our hospital, who had effort angina with suspected stable CAD. Stable CAD was defined as no recent deterioration or rest pain in the previous 6 months but angiographically documented coronary artery stenosis <50% and no previous MI. We enrolled totally 115 patients with non-significant coronary lesion, absence of >50% diameter stenosis in any coronary vessel ≥1.5 mm in diameter, into the study. Of these patients, 64 had proximal/mid segment of the LAD lesions (Group 1) and 51 had distal segments of the LAD lesions (Group 2). All participants provided written informed consent to participate in the study. The study protocol was approved by the local ethics committee, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical practice (GCP)/International Conference on Harmonization (ICH) guidelines.

Exclusion criteria included non-significant lesion in left circumflex and/or right coronary artery, >50% diameter stenosis in any coronary vessel, congestive heart failure (ejection fraction <50%), previous myocardial infarction, suspected myocarditis or pericarditis, diabetes mellitus, stroke, known peripheral atherosclerotic disease, surgical coronary intervention, other major vascular surgical procedures, percutaneous coronary angioplasty, unstable angina pectoris, impaired renal function (creatinine ≥1.4 mg/dL), unstable endocrine or metabolic diseases, patients with concomitant inflammatory diseases such as infections and autoimmune disorders, acute/chronic hepatic or hepatobiliary disease and malignancy. Patients taking corticosteroids, anti-oxidant vitamins and alcohol were also excluded from the study.

Blood sampling and laboratory methods

Blood samples of all individuals were taken from an antecubital vein following an overnight fasting state just after angiography. After centrifugation at 3000× *g* for 10 min, serum and plasma samples were frozen and stored at −80°C until an assay could be performed. Serum sLOX-1 levels were measured by a commercially available enzyme-linked immunosorbent assay kit (USCN Life Science, 430079, Wuhan, China). The detection limit for serum sLOX-1 level was 2.4 pg/mL with a coefficient of variation <5%. Analyses were performed by the immunologists, who were blinded to the condition of the samples. Triglyceride (TG), total cholesterol (Total-C), Low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) concentrations were measured by automated chemistry analyzer (Roche Diagnostics, Indianapolis, USA) using commercially available kits. We measured serum creatinine levels in all study patients and calculated the glomerular filtration rate (GFR) with MDRD formula.

Angiographic analysis

All patients underwent routine coronary angiography using the Judkins technique with digitized coronary angiography equipment (Siemens, Medical Solutions 2007, Munchen, Germany). All coronary angiograms were visually assessed by at least two experienced invasive cardiologists who were unaware of the patient's status, and a consensus was reached. For this study, we defined non-significant lesion as minimal lumen diameter stenosis <50% on the angiogram. Proximal/middle segment LAD lesions were defined as lesions from LAD ostium to beginning of second diagonal artery, and distal LAD lesions were defined as lesions from second diagonal artery to the end of the LAD.

Statistical analysis

Continuous variables were given as mean ± SD; categorical variables were defined as percentages. Comparisons between Group-1 and Group-2 were carried out using an

independent samples t test. Sensitivity and specificity values of sLOX-1 levels for predicting proximal/mid LAD lesion were estimated using receiver operator characteristic (ROC) curve analysis. The cutoff level of sLOX-1 levels were determined using MedCalc 9.2.0.1 (MedCalc Software, Mariakerke, Belgium). Correlation analyses were performed using the Pearson coefficient of correlation. SPSS 15.0 software was used for basic statistical analysis (Version 15, SPSS Inc., and Chicago, IL, USA). A value of $p < 0.05$ was accepted as statistically significant.

Results

Table 1 shows the baseline characteristics of patients in two groups. There were no significant differences between two groups in age, gender, family history, history of hypertension, and smoke. The levels of fasting glucose, GFR (with MDRD formula), total-C, LDL-C, HDL-C, and triglyceride were not differing between groups (Table 1).

Significantly higher sLOX-1 levels in proximal/mid LAD lesion group (Group 1) than distal LAD lesion group (Group 2) were shown in Fig. 1 (sLOX-1 levels were 1.07 ± 0.33 in Group 1 and 0.70 ± 0.17 in Group 2; $p < 0.001$). There were no correlations between sLOX-1 levels and fasting glucose, GFR, LDL-C, HDL-C, total-C, and triglyceride levels, separately. In Fig. 2, an ROC curve is used to identify the ability of sLOX-1 levels to predict the proximal/mid LAD lesion. The area under the ROC curve was 0.837 for the sLOX-1 levels ($P = 0.0001$). The sensitivity and specificity values of the sLOX-1 levels were 53.8% and 95.2%, respectively (cut off value was 0.68).

Table 1 The demographic and clinical characteristics of patients in two groups

	Group 1(n=64)[a]	Group 2(n=51)[b]	P value
Age (years)	58 ± 7	60 ± 9	0.1
Female (%)	40	39	0.8
Fasting glucose (mg/dL)	94 ± 9	96 ± 10	0.2
Serum creatinine (mg/dL)	0.84 ± 0.19	0.87 ± 0.16	0.3
GFR (%)	90.3 ± 8.8	90.1 ± 9.7	0.9
Lipid profile (mg/dL)			
Total-C	207 ± 25	213 ± 29	0.3
LDL-C	127 ± 19	123 ± 20	0.3
HDL-C	44 ± 10	46 ± 13	0.4
Triglyceride	196 ± 69	195 ± 76	0.9
History of (%)			
Family	59	41	0.2
HT	50	54	0.3
Smoke	48	45	0.4

Data expressed as mean ± SD or percentage

Total-C total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *DM* diabetes mellitus, *HT* hypertension, *GFR* glomerular filtration rate with MDRD formula

* $P < 0.05$ was accepted statistically significant

[a] Group 1 proximal/middle LAD lesion Group

[b] Group 2 distal LAD lesion Group

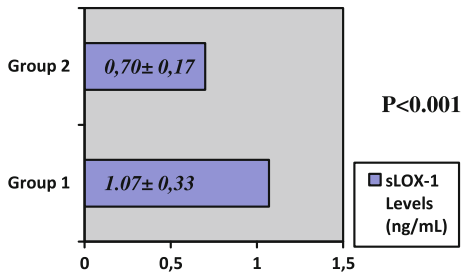

Fig. 1 The comparison of sLOX-1 levels between two groups (*Group 1* proximal/middle LAD lesion Group, *Group 2* distal LAD lesion Group, *sLOX-1* lectin-like oxidized low-density lipoprotein receptor-1) sLOX-1 levels were 1.07 ± 0.33 in Group 1 and 0.70 ± 0.17 in Group 2. $P < 0.05$ was accepted statistically significant

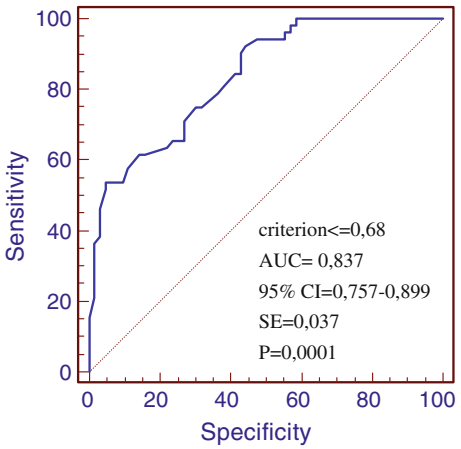

Fig. 2 ROC curve of sLOX-1 levels in study patients for localization of lesion in left anterior descending artery. *AUC* area under curve, *SE* standard error, *CI* confidence interval

Discussion

The results of this study showed that among patients with stable CAD, those with proximal/mid segment of the LAD lesions had significantly higher circulating sLOX-1 levels than those with distal segment of the LAD lesions. To the best of our knowledge, this is the first study to show that the serum levels of sLOX-1 represent a marker of atherosclerotic plaque localization in stable CAD patients. Serum sLOX-1 levels were associated plaque localization lesions that might predict vulnerable plaques. This study suggested

sLOX-1 might be a useful biomarker of coronary plaque vulnerability in patients with stable CAD.

Atherosclerosis is a chronic, progressive, dynamic, and inflammatory disease with a long asymptomatic phase. Disease progression can lead eventually to the occurrence of acute cardiovascular events such as MI, unstable angina pectoris, and sudden cardiac death. While the disease is still in a sub-clinical stage, however, several invasive and noninvasive imaging techniques, including coronary angiography, intravascular ultrasonography, B-mode ultrasonography, computed tomography, magnetic resonance imaging, and assessment of inflammatory biomarkers, have been used to detect and/or diagnose the presence of atherosclerotic lesions and its functional status, facilitate risk stratification, and measure atherosclerosis progression and regression.

Advances in recent research have provided greater understanding of the underlying pathophysiology of atherosclerosis and its clinical manifestations. Atherosclerotic plaques consist of lipids, inflammatory cells, connective-tissue elements, smooth-muscle cells, thrombi, and calcium deposits [5, 7, 10, 31]. All aspects of plaque formation and the progressive atherosclerotic process are related to inflammatory responses and atherosclerosis occurs preferentially at certain sites within the arterial tree, at the branching points of a coronary artery [5, 10]. In clinical and pathologic studies, the proximal and mid portions of the major coronary arteries have been identified as the most frequent sites of plaque rupture that have result in ACS [24–30]. In addition, Katritsis et al. [32] reported that the majority of culprit lesions on the LAD that result in ACS are located within the first 4 cm from its origin and before the second septal or the second diagonal side branch.

Atherosclerotic lesions of the proximal segment of the LAD constitute a special subgroup of CAD, given the high-risk profile [11, 12]. Patients with proximal LAD occlusion in association with low left ventricular ejection fraction have been reported to have 19-fold higher mortality than the general population [33]. Katritsis et al. [32] postulated that rupture of vulnerable plaques and subsequent development of thrombotic lesions along the coronary tree may depend on several anatomic parameters, such as proximity of side branches and bifurcations, angulation of the relevant coronary segment, and axial bending during the cardiac cycle. All these anatomic features have been correlated with hemodynamic parameters that may potentially affect plaque rupture and subsequent thrombosis [34, 35].

LDL-C is recognized as one of the primary factors in the development and progression of atherosclerosis [36, 37]. LDL-C undergoes oxidative modification in arterial walls in situ and becomes ox-LDL with atherogenic properties [38]. Proinflammatory stimuli promote LDL-C oxidative modification, and ox-LDL provokes inflammation; thus oxidative stress and inflammation in arterial walls are closely linked. Oxidative stress and subsequent inflammation have been characterized in atherosclerosis, from its beginning, such as the state of endothelial dysfunction, to its end-sequelae, such as acute MI and stroke [39]. Ox-LDL changes the secretory activities of endothelium and causes it to become dysfunctional [40]. The affected endothelium expresses a lot of surface molecules that attract circulating inflammatory cells and facilitate their migration into the subendothelial space [10]. Ox-LDL inhibits the expression of constitutive nitric oxide synthase [41], induces expression of adhesion molecules, and facilitates inflammatory cells to adhere to the intima [42]. Some of ox-LDL can be detected in circulating blood and have been shown to be elevated in ACS [43, 44].

Interactions between ox-LDL and its receptor LOX-1, a type II membrane glycoprotein, is the major receptor for ox-LDL in endothelial cells [13], appear to play key roles in ox-LDL-induced vascular dysfunction, including apoptosis of endothelial cells, and monocytes/macrophages, expression of adhesion molecules and activates the inflammatory cascade activation, which evokes atherosclerotic plaque rupture or erosion [45–48]. Expression of LOX-1 is upregulated by angiotensin II, free radicals, inflammatory cytokines, and shear stress [49–51]. Furthermore, LOX-1 activates MMPs [48] resulting in collagen degradation and initiation of plaque rupture—the most proximate cause of ACS. Many studies [52, 53] have shown that an increase in the activity and expression of MMPs plays a central role in the composition of atherosclerotic plaques. Ox-LDL, LOX-1, and MMPs have been found to be co-localized in advanced atherosclerotic plaques [43, 54]. Their interaction may lead to the instability of atherosclerotic plaques. These pathological effects of LOX-1 not only initiate atherosclerotic lesion formation, but also contribute to the vulnerability of a plaque to rupture. Circulating levels of sLOX-1 are increased in patients with unstable coronary syndromes [55]. In addition, a recent pilot study has shown that sLOX-1 predicted prognosis, such as future recurrence of ACS or death, in patients with ACS [56]. In experimental animal models, LOX-1 expression is closely associated with morphological plaque instability and cell apoptosis, as well as with the expression of MMPs and tissue factor, all of which are associated with plaque rupture and thrombus formation [57–59]. A study [60] demonstrated that LOX-1 deficiency significantly decreases the formation of atherosclerotic lesions.

Inflammatory process begins from the earliest phase of atherosclerosis, formation of fatty streak, involving the leukocyte infiltration and link between plaque formation and acute plaque rupture, leading to ACS [45]. Although

a coronary artery plaque large enough to cause significant stenosis can lead to myocardial ischemia, critical stenosis does not always occur [10, 31, 61]. Current thinking is that plaque activation rather than stenosis leads to thrombus formation and myocardial ischemia or infarction [7]. The expanding plaque may eventually become exposed due to endothelial erosion or plaque rupture, each leading to thrombosis [10, 31]. Both plaque rupture and endothelial erosion are related to increased inflammatory activity within the plaque, and the main stimulus for this inflammation is the reaction of oxidized intimal LDL and macrophages [31]. Minor episodes of endothelial erosion or plaque rupture may occur asymptomatically; however, repeated cycles of erosion or rupture, thrombosis, and repair gradually increase the size of the plaque [10].

Atherosclerosis occurs frequently at the branching points of a coronary artery [62]. A higher incidence of ruptured plaques was detected before and after bifurcation in the proximal LAD and at sites of vessel angulation in the LAD [32]. El Fawal et al. [24], in a pathologic study on 59 patients who died of MI in Glasgow, provided evidence that thrombosis are distributed in the proximal coronary vessels. In addition, in young subjects less than 40 years of age, dying of non-cardiovascular causes, vulnerable coronary plaques are concentrated proximally, and diminish with distance in all coronary arteries [25]. These observations suggest that proximal coronary plaques are more prone to rupture. Wang and colleagues [29] demonstrated that acute coronary occlusions leading to MI tend to cluster in predictable "hot spots" within the proximal third of the coronary arteries, particularly the LAD and left circumflex. A pathologic study has also demonstrated that over 50% of thin-cap fibroatherosclerotic plaques occur in the proximal portions of the major coronary arteries, another one-third in the mid portion of these arteries, and the rest distributed in distal segments [30]. Valgimigli et al. [63, 64], in intravascular ultrasound studies, have shown that plaque distance from the coronary ostium is an independent determinant of relative lipid content. Plaques located within the proximal 20 mm of coronary vessels are relatively richer in lipid content compared with those more distally located [63].

In conclusion, the present study firstly showed that sLOX-1, a biomarker for plaque formation, progression and/or destabilization; levels were associated with proximal/mid segment of the LAD lesions that might predict vulnerable plaques. These results suggested that the sLOX-1 might be a useful biomarker of plaque vulnerability in patients with stable CAD. Soluble LOX-1 can be used as a target for imaging of atherosclerotic plaque. Soluble LOX-1, the novel biochemical marker, may provide new insights into not only risk stratification but also therapeutic strategy for CAD. However, the limitation of the present study would be the relatively small sample size, and thus the present findings should be confirmed by multicenter studies with larger sample sizes.

Acknowledgments No funding supported this study.

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