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Circulating soluble lectin-like oxidized low-density lipoprotein receptor-1 levels predict percutaneous coronary intervention-related periprocedural myocardial infarction in stable patients undergoing elective native single-vessel PCI

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Abstract Percutaneous coronary intervention-related periprocedural myocardial infarction (PCI-RPMI) has now been definitively linked in large data sets to long-term adverse outcomes. It is more likely that the relationship is caused by the underlying predisposing factors that led to the PCI-RPMI, such as plaque vulnerability. Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is involved in multiple phases of vascular dysfunction, including atherosclerotic plaque formation and/or vulnerability. The purpose of this study was to determine whether soluble LOX-1 (sLOX-1) is associated with myocardial necrosis in elective native single-vessel PCI (NSV-PCI). From January 2010 to January 2012, 214 consecutive stable patients undergoing elective NSV-PCI were enrolled. Troponin T, CK and CK-MB were performed to screen for PCI-induced myocardial necrosis after the procedure, and PCI-RPMI was defined as three times the ULN of CK, which was confirmed by the elevation of the CK-MB and troponin T. According to the cardiac biomarkers result, patients were divided into two groups [PCI-RPMI(+) and PCI-RPMI(−)]. sLOX-1 levels were measured in serum by ELISA. Of the 214 patients who underwent NSV-PCI, 33 (15.4 %) patients developed PCI-RPMI. The results of this study showed that among patients undergoing elective NSV-PCI, those with PCI-RPMI had significantly higher circulating sLOX-1 levels than those without (167 ± 89 vs. 99 ± 68 pg/mL; $p < 0$ 0.001). There were high correlations between sLOX-1 levels and CK and CK-MB values ($r = 0.677$ and $r = 0.682$, respectively; $p < 0.001$). Our study demonstrated that circulating sLOX-1 levels were associated with PCI-RPMI, which might predict periprocedural myocardial necrosis in elective NSV-PCI. Importantly, the study speculates that the level of sLOX-1 may help to identify patients at risk for PCI-RPMI before the procedure. sLOX-1 may provide new insights into not only risk stratification, but also therapeutic strategies for elective PCI.

Keywords Elective percutaneous coronary intervention · Native coronary artery · Periprocedural myocardial infarction · Soluble lectin-like oxidized low-density lipoprotein receptor-1

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Introduction

Percutaneous coronary intervention (PCI) has become the most common form of coronary revascularization worldwide [1]. Although generally a safe procedure, PCI does have multiple associated risks, including coronary dissection, the no-reflow phenomenon, and abrupt vessel closure. These complications are obviously undesirable and associated with negative follow-up outcomes, but an even more frequent and important contributor to the morbidity and mortality associated with PCI is periprocedural myocardial infarction (PMI) [2]. The definition of PMI was standardized with a post-procedure elevation of cardiac biomarkers more than three times the 99th percentile of the upper limit of normal (ULN) defined as PCI-related PMI (PCI-RPMI; type 4a) [3]. An increase of cardiac biomarkers has been shown to occur in 5–30 % of cases after otherwise successful PCI [4, 5]. Multiple data sets have now definitively

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demonstrated that PCI-RPMI is associated with short-, intermediate-, and long-term adverse outcomes, most notably, mortality [6, 7]. During and after PCI, a number of factors have been associated with PCI-RMI, which can broadly be categorized as (a) lesion-related, (b) patient-related, and (c) procedure-related factors. Most notably, lesion-related factors, such as disease burden [8, 9], calcification, lesion morphology, plaque vulnerability, and presence of thrombus [10], can predict myonecrosis.

Lectin-like oxidized low-density lipoprotein (LDL) receptor-1 (LOX-1) is a receptor for atherogenic oxidized LDL (ox-LDL) in advanced human atherosclerotic plaques [11]. LOX-1 has been implicated in vascular inflammation and atherosclerotic plaque formation and vulnerability [12]. The expression of LOX-1 in endothelial cells is relatively lower in the basal condition, but it can be induced by proinflammatory cytokines in vitro [13–15] and in proatherogenic conditions in vivo [16, 17]. LOX-1 is cleaved at the membrane-proximal extracellular domain by certain proteases [18, 19], which may also be associated with plaque vulnerability or rupture, resulting in soluble LOX-1 (sLOX-1) release into the circulation, which can be measured in the serum [19]. 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 assessment. In addition, LOX-1 induces free radical generation [20], apoptosis of endothelial cells and monocytes/macrophages [21], and expression of adhesion molecules [22] and activates the inflammatory cascade [23]. These pathological effects of LOX-1 not only initiate atherosclerotic lesion formation, but may also contribute to the vulnerability of a plaque to rupture. We therefore sought to clarify the link between circulating sLOX-1 levels and myonecrosis in stable patients undergoing elective native single-vessel PCI (NSV-PCI). The present study was the first to evaluate the relationship between sLOX-1 and PCI-RMI in stable patients undergoing elective NSV-PCI.

Materials and methods

Patient population

From January 2009 to December 2010, 214 consecutive stable patients with de novo lesions referred to our catheterization laboratory for elective PCI of a single-vessel lesion in a major (diameter $\geq$2.5 mm) native coronary artery were considered for our study. Enrolled patients who were at least 18-years-old were eligible for the study if they had normal troponin T, CK and CK-MB values before the procedure and were in stable condition. Clinical history was obtained to ensure clinical stability before enrollment. Stable patients were defined as those with no recent deterioration of pain in the previous 2 months or without rest angina in the previous 48 h and angiographically documented coronary artery stenosis at levels of 70–95 % and with no ECG changes before PCI. Further criteria for inclusion were that the PCI procedure was successful and an optimal final result was obtained, i.e., a thrombolysis in myocardial infarction (TIMI) flow grade 3 in the treated vessel with a residual stenosis <20 %. At the end of PCI, antegrade coronary flow in the target vessel was assessed according to TIMI classification [24]. All participants provided written informed consent to participate in the study. The protocol was approved by the local ethics committee.

Exclusion criteria included: the presence of major ($\geq$1.5 mm) side branch occlusion, flow-limiting dissection, distal embolization of a large thrombus, no-reflow phenomenon, untreated diffuse vasospasm, unsuccessful procedures, target lesion in the left main coronary artery, target lesion in saphenous graft, bifurcation lesions, patients with total and/or subtotal occlusions, use of GPIIb/IIIa inhibitors during the procedure, congestive heart failure (ejection fraction <50 %), suspected myocarditis or pericarditis during the procedure, untreated diabetes mellitus, unstable angina pectoris, non ST-segment elevation myocardial infarction, impaired renal function (creatinine $\geq$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, contraindications to aspirin or clopidogrel, and inability to provide informed consent. 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 before the procedure; a routine peri-interventional assessment of cardiac biomarkers (troponin T, CK and CK-MB) was performed to screen for PCI-induced myocardial necrosis up to 24 h (at 6 h intervals) after PCI or until the highest value of troponin T, CK and CK-MB was measured. Total CK activity (normal $\leq$195 IU/L) and CK-MB activity (normal $\leq$24 IU/L) were measured on a Hitachi 917 (Boehringer, Mannheim, Germany) analyzer with an automatic enzyme immunoassay method. PCI-RPMI was defined as three times the ULN of CK, which was confirmed by the elevation of the MB fraction of CK [3]. The highest troponin T, CK and CK-MB value within 24 h post-PCI was used for analysis. According to the cardiac biomarkers result, patients were divided into two groups

[PCI-RPMI(+) and PCI-RPMI(−)]. For assessment of sLOX-1, after centrifugation at 3,000×*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. 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 an automated chemistry analyzer (Roche Diagnostics, Indianapolis, USA) by using commercially available kits. Blood samples for troponin T were measured with Roche kits in Elecsys/e 411 Roche device (Roche Diagnostics, Mannheim, Germany). The values greater than 0.10 μg/L were considered to be positive.

Percutaneous coronary intervention

All PCI procedures were performed according to standard clinical practice and with approved devices by the femoral approach with digitized coronary angiography equipment (Siemens, Medical Solutions 2007, Munchen, Germany). We used iohexol (Omnipaque, Nycomed Ireland, and Cork, Ireland) as the contrast agent during intervention in all patients. All patients were treated with aspirin (300 mg) and clopidogrel (600 mg) on admission unless they had already started in the days preceding PCI. Patients received intravenous unfractionated heparin (100 IU/kg), followed by additional boluses as needed to maintain an activated clotting time >300 s; intracoronary nitroglycerin (200 μg) was administered before PCI in all patients. Other cardiac medications were left at the discretion of the treating physician. All intervention procedures were visually assessed by at least two experienced invasive cardiologist who were unaware of the patients' status, and a consensus was reached. For this study, we defined significant lesion as minimal lumen diameter stenosis ≥70 % on the angiogram.

Statistical analysis

Continuous variables were given as mean ± SD; categorical variables were defined as percentages. Comparisons between two groups were carried out using an independent-samples *t* test and χ^2 test. Comparisons between more than two subgroups were applied with One-way ANOVA test. 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

Of the 214 patients who underwent elective NSV-PCI, according to CK and CK-MB value rise after PCI, periprocedural myocardial necrosis (>3 time the ULN of CK and/or CK-MB value) was detected in 33 patients (15.4 %). The baseline characteristic properties of study patients were summarized in Table 1. All patients had baseline troponin T, CK and CK-MB values within normal limits before the procedure. There were no significant differences between the PCI-RPMI(+) and PCI-RPMI(−) groups with respect to sex distribution, age, frequencies of major coronary risk factors (i.e., diabetes mellitus, hypertension, dyslipidemia, smoking, and family history of coronary artery disease), fasting glucose, HgA1c, serum creatinine, Total-C, LDL-C, HDL-C, TG, heart rate, systolic blood pressure, and diastolic blood pressure ($p > 0.05$ for all). We showed the medication of patients before PCI in Table 2. There were no significant differences between the two groups. Troponin *T* values were 0.78 ± 0.41 μg/L in PCI-RPMI(+) group and 0.07 ± 0.09 μg/L in PCI-RPMI(−) group ($p < 0.001$). CK values were 778 ± 144 IU/L in PCI-RPMI(+) group and 292 ± 111 IU/L in PCI-RPMI(−) group ($p < 0.001$) (Fig. 1). CK-MB levels were 76 ± 15 IU/L in the PCI-RPMI(+) group and 28 ± 9 IU/L in the PCI-RPMI(−) group

Table 1 The baseline characteristic properties of study patients

	PCI-RPMI(+) ($n = 33$)	PCI-RPMI(−) ($n = 181$)	*p* value
Age (years)	60 ± 7	58 ± 10	0.2
Female (%)	36	37	0.5
History of (%)			
Diabetes mellitus	18	20	0.5
Hypertension	42	47	0.3
Smoke	66	65	0.7
Family history of CAD	24	24	0.5
Dyslipidemia	45	50	0.3
Fasting glucose (mg/dL)	108 ± 26	114 ± 39	0.2
HgA1c (%)	5.8 ± 0.9	6.0 ± 1.1	0.3
Creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.1	0.6
Triglyceride (mg/dL)	188 ± 71	195 ± 61	0.5
Total cholesterol (mg/dL)	208 ± 23	206 ± 24	0.6
LDL-C (mg/dL)	132 ± 16	127 ± 19	0.1
HDL-C (mg/dL)	40 ± 8	43 ± 11	0.1
Heart rate (beat/min)	82 ± 11	84 ± 11	0.4
SBP (mmHg)	128 ± 20	134 ± 19	0.1
DBP (mmHg)	75 ± 11	77 ± 11	0.4

$p < 0.05$ was accepted as statistically significant

CAD coronary artery disease, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

Table 2 Preprocedural medication of study patients

Drugs	PCI-RPMI(+) ($n = 33$)	PCI-RPMI(−) ($n = 181$)	p value
ASA (%)	45	43	0.4
Statin (%)	27	42	0.08
ACE/ARB (%)	39	39	0.5
CCB (%)	36	29	0.2
Beta blocker (%)	30	34	0.3

$p < 0.05$ was accepted as statistically significant

ASA acetylsalicylic acid, *ACE* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CCB* calcium channel blocker

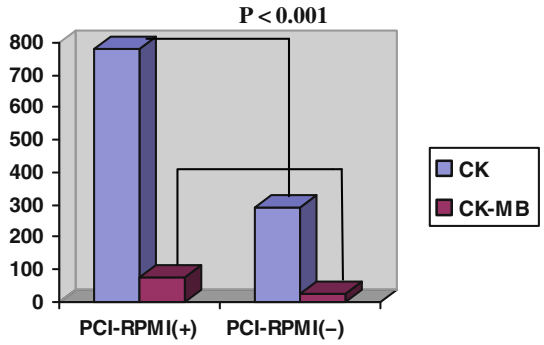

Fig. 1 The comparison of CK and CK-MB levels between PCI-RPMI(+) and PCI-RPMI(−) groups in patients undergoing elective native single-vessel PCI (CK values were 778 ± 144 IU/L in PCI-RPMI(+) group and 292 ± 111 IU/L in PCI-RPMI(−) group; $p < 0.001$. CK-MB levels were 76 ± 15 IU/L in the PCI-RPMI(+) group and 28 ± 9 IU/L in the PCI-RPMI(−) group; $p < 0.05$ was accepted as statistically significant

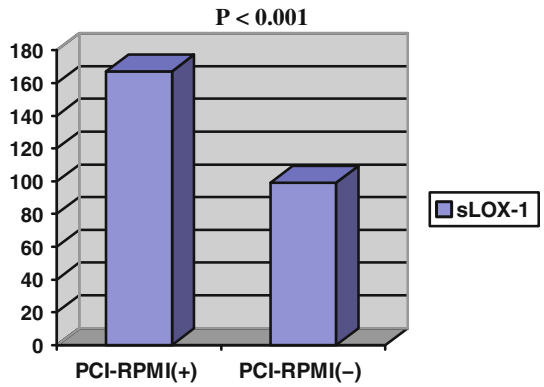

Fig. 2 The comparison of sLOX-1 levels between PCI-RPMI(+) and PCI-RPMI(−) groups in patients undergoing elective native single-vessel PCI (167 ± 89 pg/mL in the PCI-RPMI(+) group and 99 ± 68 pg/mL in the PCI-RPMI(−) group; $p < 0.05$ was accepted as statistically significant

($p < 0.001$) (Fig. 1). The mean sLOX-1 levels were significantly higher in the PCI-RPMI(+) group than patients in the PCI-RPMI(−) group (167 ± 89 and 99 ± 68 pg/mL, respectively; $p < 0.001$) (Fig. 2). The mean sLOX-1 levels were similar according to the target vessel distribution (110 ± 70 pg/mL in LAD, 109 ± 82 pg/mL in CX and 108 ± 78 pg/mL in RCA; $p = 0.9$).

The mean lesion length and reference vessel diameters were similar between the two groups (lesion lengths were 20 ± 4 mm in the PCI-RPMI(+) group and 19 ± 5 mm in the PCI-RPMI(−) group; $p = 0.4$ and reference diameters were 2.8 ± 0.3 mm in the PCI-RPMI(+) group and 2.9 ± 0.3 mm in the PCI-RPMI(−) group; $p = 0.2$). Final balloon pressures were similar between two groups (16.1 ± 1.9 mmHg in the PCI-RPMI(+) group and 16.4 ± 1.9 mmHg in the PCI-RPMI(−) group; $p = 0.5$). The use of bare metal and drug-eluting stents, and the diameter and length of the implanted stents were also similar in both groups ($p > 0.5$).

The sLOX-1 levels were highly positive correlated with CK and CK-MB value levels ($r = 0.677$, $p < 0.001$ and $r = 0.682$, $p < 0.001$, respectively). The troponin T levels were significantly positive correlated with sLOX-1 levels ($r = 0.242$, $p < 0.001$). When we divided the patients into three group according to the lesion locations as proximal, middle, and distal lesions, the mean sLOX-1 levels were 122 ± 89 pg/mL in proximal ($n = 75$), 108 ± 68 pg/mL in middle ($n = 115$), and 77 ± 48 pg/mL ($n = 24$) in distal segment lesions ($p = 0.03$).

Discussion

The results of this study showed that among stable patients undergoing elective NSV-PCI, those who represented PCI-RPMI had significantly higher circulating sLOX-1 levels than those unrepresented. The other finding of the present study was that serum sLOX-1 levels were independently correlated with the amount of cardiac biomarkers (CK and CK-MB). To the best of our knowledge, this is the first study to show that the serum level of sLOX-1 represents a marker of PCI-RPMI in stable patients undergoing elective NSV-PCI. Serum sLOX-1 levels were associated with PCI-RPMI, which might predict periprocedural myocardial damage. This study suggested sLOX-1 might be a useful biomarker of periprocedural myocardial damage in stable patients undergoing elective NSV-PCI.

During the past two decades, coronary stenting either with predilatation (conventional stenting) or without predilatation (direct stenting) has become the leading type of PCI and accounts for approximately 70 % of all catheter-based procedures [25, 26]. Coronary stenting is considered a well-established technique to improve outcomes of PCI and to reduce the incidence of emergency coronary artery bypass grafting after PCI [27]. The worldwide use of this technique has rapidly increased in recent years [28]. With technological advances in PCI, procedural

complications and long-term outcomes have significantly improved, yet PCI-RPMI remains relatively common after successful PCI. An increase of cardiac enzymes has been shown to occur in 5–30 % of cases after otherwise successful PCI [4, 5]. This elevation of cardiac enzymes is indicative of myocardial damage, and according to the new criteria, should be labeled as a PCI-RPMI. The most common definition of PCI-RPMI is a CK elevation >3 times the ULN [5]. CK and CK-MB, the most thoroughly validated biomarker for periprocedural myocardial damage, is generally regarded as the reference standard for the diagnosis of myocardial necrosis and is commonly used to monitor myocardial necrosis after PCI [29, 30].

Multiple studies have shown a proportional relationship between the level of periprocedural CK and/or CK-MB elevation and the risk of adverse outcome during follow-up. A meta-analysis of 23,230 patients undergoing PCI in seven large prospective trials showed that long-term mortality risk increases at any level above normal periprocedural CK-MB [31]. The evaluation of platelet IIb/IIIa inhibition for prevention of ischemic complication (EPIC) trial conclusively demonstrated the association between CK elevation and three-year mortality [32]. Several other studies have corroborated the relationship between PMI and short-, intermediate- and long-term outcome. In a study of 15,637 patients undergoing elective PCI, mortality at 10 years was significantly higher in those with CK elevations >3 times the ULN [33]. After excluding in-hospital and 30 day deaths, this degree of CK elevation remained an independent predictor of death. Even CK elevation 1.5–3.0 times the ULN is associated with higher mortality, with each 100 U/L increment of CK associated with a relative risk of cardiac mortality of 1.05 [34].

Revascularization procedures resulting in direct instrumentation and manipulation of the coronary arterial vasculature predispose patients to ischemic events that can lead to myocardial necrosis. During and after PCI, a number of factors have been associated with periprocedural MI, which can broadly be categorized as (a) patient-related, (b) lesion-related, and (c) procedure-related factors. Patient-related factors, including multivessel disease, evidence of systemic atherosclerosis, reduced left ventricular ejection fraction, diabetes mellitus, older age, and chronic kidney disease, increase the risk of periprocedural CK-MB release by 1.3-fold to 1.8-fold [35–38]. The clinical syndrome on presentation also affects risk, with enzyme negative patients with acute coronary syndromes having up to a 40 % incidence of periprocedural enzyme elevations [38]. Lesion-related factors, such as disease burden, [8], calcification, lesion morphology, plaque vulnerability, and presence of thrombus [10], predict increased periprocedural enzyme release [39, 40]. Atheromatous plaque burden measured with IVUS before PCI has been shown to be proportional to procedural enzyme release [8]. Procedure-related variables such as device selection, atherectomy [41], aggressive stent expansion resulting in plaque extrusion [42], side branch occlusion [10, 43], side branch stenting [44], and angiographic complications (including distal embolization, [45], coronary dissection [35, 46], no-reflow phenomenon [35, 40, 47], vasospasm [5] and unsuccessful procedures [48]) are all associated with PMI. In totality, these risk factors identify patients with an increasing atherosclerotic disease burden and increased thrombotic risk [47, 49] that predisposes them to either macrovascular complications (side branch occlusion or macroembolization) or microvascular obstruction (distal embolization of microparticles), unifying the pathophysiologic basis of myocardial necrosis after intervention [47, 49, 50].

Recent clinical studies indicate that patients with preprocedural elevations of C-reactive protein serum concentrations are at higher risk of adverse cardiac events during follow-up after PCI, particularly ischemic events during the first post-procedural days [51, 52]. Furthermore, a combination of anatomic lesion characteristics with the inflammatory index was found to be superior to procedural risk assessment by the American College of Cardiology/American Heart Association lesion criteria alone [52]. Patients with more complex target lesions are at higher risk of these events [8, 35].

Myocardial tissue damage in patients who have undergone successful PCI is mainly related to distal vessel thrombosis, embolization of plaque debris, and platelet aggregates [50, 53]. Most PCI-related infarcts are small and result from microemboli from the atherosclerotic plaque that has been disrupted during angioplasty and/or stenting [4]. Thereby, myocardial necrosis occurring during the intervention may represent vascular bed instability. It is likely that patients who develop coronary emboli and infarcts during/after PCI have atherosclerotic lesions that are apparently unstable and continue to represent a substrate for plaque rupture with subsequent thrombosis resulting in adverse events [54].

LOX-1 is a receptor for atherogenic ox-LDL [11]; its expression is induced by factors related to atherogenesis and plaque vulnerability, such as proinflammatory cytokines [14], angiotensin II [55], high glucose [56] and ox-LDL [57], which is expressed on the surface of intimal smooth muscle cells [58] and lipid-laden macrophages [58, 59] in advanced human atherosclerotic plaques, which may also be associated with plaque vulnerability or rupture [60]. Interactions between Ox-LDL and its receptor, LOX-1, appear to play key roles in Ox-LDL-induced vascular dysfunction, including cells apoptosis and matrix metalloproteinase production and activation, which evokes atherosclerotic plaque rupture or erosion [11, 61]. LOX-1 expression levels significantly correlated with

atherosclerotic plaque vulnerability, as examined by immunohistochemical studies in an animal model of atherosclerosis [62]. LOX-1 induces free radical generation [20], apoptosis of endothelial cells and monocytes/macrophages [21], and expression of adhesion molecules [22] and activates the inflammatory cascade [23, 63] and platelets [64]. LOX-1 binding to ox-LDL enhances nitric oxide catabolism as a result of superoxide generation and decreases nitric oxide release via attenuated endothelial nitric oxide synthase activity [65].

These pathological effects of LOX-1 not only initiate atherosclerotic lesion formation, but also contribute to the vulnerability of a plaque to rupture. Furthermore, LOX-1 activates matrix metalloproteinase [66], resulting in collagen degradation and initiation of plaque rupture—the most proximate cause of acute coronary events. Circulating levels of sLOX-1 are increased in patients with unstable coronary syndromes [67]. On the other hand, the plasma levels of ox-LDL are related to the presence of angiographically detected complex and thrombotic lesion morphology in patients with unstable angina [68]. Zhao et al. [69] demonstrated that serum sLOX-1 levels were associated with angiographically complex coronary lesions that might predict vulnerable plaques in patients with coronary artery disease. In addition, some clinical and experimental data suggest that statins may exert anti-thrombotic effects, independent of cholesterol reduction, by affecting the vulnerability of plaque as well as platelet function [67, 70]. Furthermore, we know that pravastatin reduces expression of LOX-1 in human coronary artery endothelial cells [71].

In conclusion, to the best of our knowledge, our study demonstrated for the first time that serum sLOX-1 levels were associated with PCI-RPMI, which might predict periprocedural myocardial damage in stable patients undergoing elective NSV-PCI. These results suggested that the sLOX-1 might be a useful biomarker of periprocedural myocardial damage in stable patients undergoing elective NSV-PCI. sLOX-1 may appear to be a potential biomarker for stratifying patients into risk categories, which could lead to improved patient or physician adherence to risk-reducing behaviors or intervention techniques. Importantly, the study speculates that the level of sLOX-1 may help to identify patients at risk for PCI-RPMI before PCI procedure. However, further large scale studies are needed to more clearly define the significance of these findings.

Conflict of interest None.

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