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Regular paper

Evaluation of soluble lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1) and sLOX-1/oxidized LDL ratio as novel biomarkers of acute coronary syndrome

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The lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is involved in the pathophysiology of atherosclerosis and acute coronary syndromes (ACS). In patients with acute coronary syndrome, circulating soluble LOX-1 (sLOX-1) levels are dramatically elevated. This study aimed to assess sLOX-1 levels in acute coronary syndromes and determine the ratio of sLOX-1 and oxidative LDL in cases of myocardial infarction and unstable angina pectoris and the ROC curve for this ratio sLOX-1. A case-control study was conducted at the department of chemistry and biochemistry, college of medicine, Al-Nahrain University, Baghdad, Iraq, from September 2020 to January 2021. In a total of 90 subjects (30 patients with myocardial infarction within the first six hours of chest pains, 30 patients with unstable angina pectoris, and 30 healthy donors). The ELISA technique measured concentrations of sLOX-1 and oxidized LDL. In addition, Troponin and highly sensitive C reactive protein were measured by the same technique (Fluorescence immune assay), and lipid profile was measured using the Spectrophotometer technique. The median level of sLOX-1 in MI group was 476.17 pg/ml (90.88–675.4 pg/ml) which was significantly higher than that of UA patients (median=289.1 pg/ml [62.74–585.43 pg/ml]) and controls (median=144.52 pg/ml [79.17–283.83 pg/ml]) with highly significant differences and the median sLOX-1/OX-LDL ratio in patients with MI was 64.6 (range 15.17–100.15) which was significantly higher than either patients with UA (median=37.6 [7.06–88.65]) or controls (median=25.29 [12.7–43.04]). There were elevated levels of sLOX-1 in acute coronary syndromes. The sLOX-1/oxidized LDL ratio also strongly indicated the diagnosis and a discriminatory force on the ROC curve for myocardial infarction.

Keywords: Acute coronary syndrome, Soluble Lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1), Oxidized low-density lipoprotein, sLOX-1/ox-LDL ratio, Atherosclerosis

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Abbreviations: ACS, Acute Coronary Syndrome; STEMI, ST Elevation myocardial infarction; NSTEMI, Non- ST Elevation myocardial infarction; GAG, Glycosaminoglycans; CAD, Coronary Artery Disease

INTRODUCTION

In developing countries, acute coronary syndrome (ACS) is one of the leading causes of death and morbidity. An early and correct diagnosis of ACS will boost the prognosis by allowing for immediate care. The acute coronary syndrome refers to disorders ranging from unstable angina to ST-elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI) (Dekker *et al*., 2020). ACS is typically caused by atherosclerotic plaque breakup. However, superficial plaque degradation can also be caused by subsequent thrombus formation, leading to myocardial necrosis and elevated myocardial enzyme levels in the blood (Mashayekhi *et al*., 2018). Atherosclerosis is a chronic inflammatory condition characterized by the accumulation of lipid and inflammatory cell deposits in the walls of medium and wide arteries (Kattoor *et al*., 2019; AL- Shamma, 2020). Atherosclerosis begins with the ionic-based binding and trapping of atherogenic lipoproteins by transformed proteoglycans; specifically, biglycan with hyper elongated glycosaminoglycan (GAG) chains cause other lipid deposition diseases (Tian *et al*., 2019). As long as the arteries are healthy and atherosclerotic plaques do not block more than 40% of the blood vessel lumen, atherosclerosis may go asymptomatic (Marchio *et al*., 2019; Qazmooz *et al*., 2021). Vascular endothelial dysfunction, in which a weakened endothelium becomes more permeable, is one of the first events in ATS. This process allows lipids to enter the arterial wall, triggering an anti-inflammatory response involving immune cytes from the peripheral blood, which could then adhere to endothelium lesions (Gimbrone & García-Cardeña, 2016; Wu *et al*., 2017). LOX-1 (lectin-like oxidized low-density lipoprotein receptor-1) is a 50-kDa type II transmembrane protein with a 273-amino-acid chain that belongs to the C-type lectin superfamily structurally (Barreto *et al*., 2020), which is a scavenger receptor of the class E family that mainly binds oxidized low-density lipoprotein (ox-LDL). Evidence indicates that LOX-1 plays a crucial role in endothelial dysfunction, atherogenesis, and plaque rupture during the atherosclerotic phase; because of its critical position in the pathophysiology of atherosclerosis, LOX-1 may be used as a CAD therapeutic goal. LOX-1's extracellular domain can be cleaved by proteases and released into the bloodstream as a soluble form known as soluble LOX-1 (sLOX-1) (Pothineni *et al*., 2017; Zhao *et al*., 2019). sLOX-1 could be a useful marker for detecting ACS early on. While LOX-1 expression is higher in atherosclerotic-related diseases and is increased by pro-inflammatory stimuli, serum sLOX-1 levels were significantly higher in ACS patients than subjects without ACS when evaluated in subjects undergoing coronary angiography (CAG) (Pirillo & Catapano, 2013). Scavenger receptors (SRs) such as SR-A, CD36, and LOX-1 on the surface of endothelial cells (ECs) pick up oxidized-LDL (ox-LDL) in circulation and transport it into the vascular media. LOX-1 imbibes ox-LDL and causes foam

Table 1. Demographic characteristics of the study population

Variables	UA (n=30)	MI (n=30)	Controls (n=30)	*p*-value
Age, years Mean ±S.D. Range	55.57±7.44 40–65	54.2±8.36 40–65	52.9±8.86 40–65	0.459
Gender Male Female	16 (53.33%) 14 (46.67%)	23 (76.67%) 7 (23.33%)	16 (53.33%) 14 (46.67%)	0.101

cells to develop in monocytes/macrophages and vascular smooth muscle cells (VSMCs). In a pro-inflammatory setting, the expression of SRs is upregulated (Ding *et al.*, 2020). Therefore, this study aims to assess the level of sLOX-1 in acute coronary syndrome and determine the ratio of sLOX-1 and oxidative LDL in cases of myocardial infarction and unstable angina pectoris.

MATERIALS AND METHODS

A case-control study was conducted at the Department of Chemistry and Biochemistry at the College of Medicine, Al-Nahrain University. The samples were taken from the Department of Cardiology in Al-Imamine Al-kadhimyain Medical City and Ibn Al-Nafees Hospital in Baghdad from September 2020 to January 2021.

A Total of ninety subjects were divided into three groups. Sixty patients in this group will be divided into two groups of thirty patients. One group with myocardial infarction within the first six hours of chest pains, and the second group of patients with unstable angina pectoris. After obtaining the approval, patients were selected according to the inclusion criteria with the age range of 40–65 years. The Control group included thirty healthy people after obtaining approval. Patients with ACS who received cardiopulmonary resuscitation before admission, patients with the inflammatory disorder, pregnancy, and cerebrovascular disease within three months were excluded. The Institutional Review Board approved the research protocol and all materials included in this study at the College of Medicine of the University of Al-Nahrain. All enrolled patients were required to complete a standardized questionnaire to collect comprehensive data on medical and family history, medication use, smoking status, body weight and height, systolic and diastolic blood pressure.

Sample collection

Five ml of blood samples were drawn from the patients and the control group. The samples were collected in a gel tube and then left for 10 minutes at 37°C until it clotted and then placed in the centrifuge for 5 min at 800×*g* to obtain the serum to measure soluble lectin-like oxidized low-density lipoprotein receptors-1, oxidized low-density lipoprotein, cholesterol, Triglyceride, HDL, LDL, VLDL, hs-CRP and Troponin I.

Concentrations of sLOX-1 and oxidized LDL were measured with the quantitative sandwich enzyme immunoassay technique and enzyme-substrate chromogenic reaction by ELISA kit according to a manufacturer's protocol (CUSABIO Co). Troponin was measured with AFIAS-6 (atomic fluorescence immune assay) manufactured by Boditech (origin in Korea) at the detection range of 0.01–15.00 ng/ml.

Lipid profile was measured by cobas® c111 full atomic, and hs-CRP was measured with ichroma™ II.

Statistical analysis

Statistical analysis was performed using SPSS statistical software, version 25 (IBM Corporation, USA). Quantitative variables were subjected to a normality test (Shapiro Wilk test). Variables with normal distribution were presented as mean ± standard deviation (S.D.) and compared by Student *t*-test when there were two groups or analysis of variance (ANOVA) when there were more than two groups. Those with non-normal distribution were expressed as median and range and compared by Mann Whitney U-test with two groups, or Kruskal Wallis test with more than two groups. Correlations between biomarkers with other variables were performed with two-tailed Spearman's correlation analysis. A significant level of statistics was considered for all tests when $p<0.05$ (Peat & Barton, 2008).

RESULTS

Demographic Characteristics of the Study Population

The mean age of the patients with UA was 55.57±7.44 years which did not differ significantly from that of MI patients (54.2±8.36 years) or controls (52.9±8.86 years). More than three-fourths of the patients in the MI group were males compared with 53.33% in the UA group and controls. However, the differences were not significant as listed in Table 1.

The median level of sLOX-1 in MI group was 476.17 pg/ml (90.88–675.4 pg/ml) which was significantly higher than that of UA patients (median=289.1 pg/ml [62.74–585.43 pg/ml]) and controls (median=144.52 pg/ml [79.17–283.83 pg/ml]) with highly significant differences. Although, patients with UA had higher level of OX-LDL (median=7.28 mU/ml [2.62–33.18 mU/ml]) than either MI patients (median=6.65 mU/ml [5.44–5.56 mU/ml]) or controls (median=6.52 mU/ml [4.25–8.26 mU/ml]), the differences were not significant. Patients with MI, *per se*, demonstrated significantly much higher level of troponin than controls (median=15.0 ng/ml [0.03–20.0 ng/ml] *versus* median=0.04 ng/ml [0.01–0.2 ng/ml]). Interestingly, hs-CRP showed a remarkable variation between the different groups. In Patients with MI, the median level of hs-CRP was 70.9 mg/L (17.46–246.1 mg/L) which was significantly higher than that of UA patients (median=8.68 mg/L [5.56–23.0 mg/L]). UA patients, in turn, had higher level than control group (median=3.11 mg/L [1.19–4.8]) with a highly significant difference the median sLOX-1/OX-LDL ratio in patients with MI was 64.6 (range 15.17–100.15) which was significantly higher than either patients with UA (median= 37.6 [7.06–88.65]) or controls (median=25.29 [12.7–43.04]) as shown in Table 2.

Table 2. Serum levels of biochemical markers in different groups

Variables	UA (n=30)	MI (n=30)	Controls (n=30)	*p*-value‡
Troponin, ng/ml				
Mean ±S.D.	–	13.79±4.2	0.068±0.071	
Median		15.0	0.04	<0.001
Range		0.03–20.0	0.01–0.2	
OX-LDL, mU/ml				
Mean ±S.D.	10.11±7.35	6.78±0.82	6.56±1.17	
Median	7.28	6.65	6.52	0.068
Range	2.62-33.18	5.44–5.56	4.25–8.26	
sLOX-1, pg/ml				
Mean ±S.D.	303.28±147.46[a]	405.47±192.75[a]	159.0±48.83[b]	
Median	289.1	476.17	144.52	<0.001
Range	62.74–585.43	90.88–675.4	79.17–283.83	
sLOX/OX-LDL ratio				
Mean ±S.D.	38.0±22.35[a]	59.61±28.06[b]	24.97±8.38[a]	
Median	37.6	64.6	25.29	<0.001
Range	7.06–88.65	15.17-100.15	12.7–43.04	
hs CRP, mg/L				
Mean ±S.D.	9.38±3.39[a]	80.0±52.06[b]	3.09±1.05[c]	
Median	8.68	70.9	3.11	<0.001
Range	5.56–23.0	17.46–246.1	1.19–4.8	

Table 3. Lipid profile in different groups

Variables	UA (n=30)	MI (n=30)	Controls (n=30)	*p*-value‡
TC, mg/dl				
Mean ±S.D.	162.68±44.92	181.06±43.29	164.91±37.75	
Median	155.8	184.95	173.0	0.116
Range	95–254	66.9–256	76–236	
TG, mg/dl				
Mean ±S.D.	155.23±64.73	194.0±109.52	143.36±38.7	
Median	158.5	159.35	139.15	0.191
Range	49–275	45–536	75–218	
HDL, mg/dl				
Mean ±S.D.	36.04±5.37[a]	36.86±8.91[a]	41.94±5.39[b]	
Median	38.75	35.65	40.05	0.003
Range	25–44	23.6–53.2	34–55	
LDL, mg/dl				
Mean ±S.D.	95.48±35.84	102.35±35.23	94.08±35.08	
Median	89.2	107.95	99.0	0.657
Range	47.6–172.8	34.2–173.4	17.6–161	
VLDL, mg/dl				
Mean ±S.D.	31.3±13.3	38.78±21.89	35.26±38.98	
Median	31.7	31.84	29.7	0.247
Range	9.8–55	9.1–107.3	15–238	

Lipid Profile

Table 3 shows the lipid profile in the three groups. Data regarding the components of lipid profile were found to be non-normally distributed. Accordingly, a nonparametric Kruskal Wallis test was used to compare the medians between different groups. TG, TG, LDL, and VLDL were comparable between different groups with no significant differences. However, the median serum level of HDL in controls was 40.05 mg/dl (range 34–55 mg/dl), which was significantly higher than that of the UA group (38.75 mg/dl, range 25–44 mg/dl) and MI group (35.65 mg/dl, range 23.6–53.2 mg/dl).

Diagnostic Value of the Biomarkers

Between UA and MI

sLOX-1/OX-LDL ratio, the AUC was 0.714, 95%CI=0.583–0.846, p=0.004. The sensitivity and specificity of the test at a cut-off value of sLOX-1/OX-LDL=42.46 were 70% and 67%, respectively, and for hs-CRP, the AUC was 0.998, 95%CI=0.992–1.0, p<0.001. The sensitivity and specificity of the test at a cut-off value of CRP=23.5 mg/L were 93% and 100%, respectively, as shown in Fig. 1.

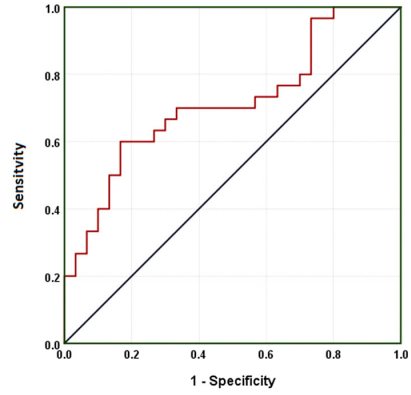

Figure 1. The receiver operating characteristic (ROC) curve for the sLOX-1/OX-LDL ratio between unstable angina and myocardial infarction patients

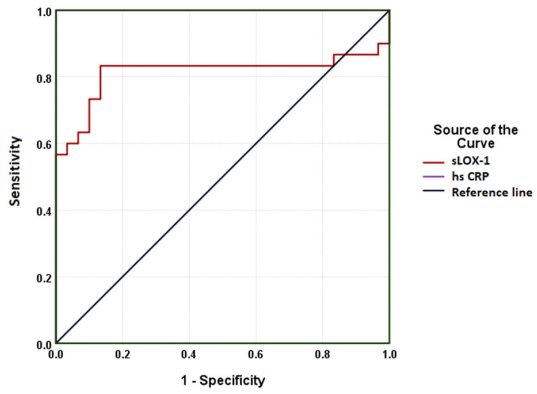

Figure 2. The receiver operating characteristic (ROC) curve for sLOX-1 and hs CRP levels between unstable angina patients and the control group

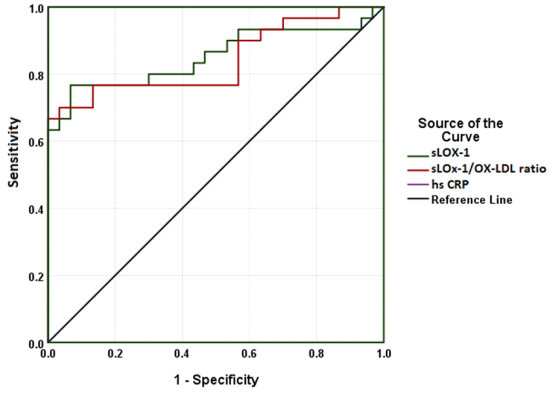

Figure 3. The receiver operating characteristic (ROC) curve for sLOX-1, sLOX1/ Ox-LDL ratio, and hs CRP levels between myocardial infarction patients and the control group.

Between UA and Controls

For sLOX-1, the AUC was 0.813, 95%CI=0.685-0.942, $p<0.001$. The sensitivity and specificity of the test at a cut-off value of sLOX-1=210.35 pg/ml were 83% and 87%, respectively, as shown in Fig. 2.

Between MI and controls

For sLOX-1, the AUC was 0.852, 95%CI=0.748–0.957, $p<0.001$. The sensitivity and specificity of the test at a cut-off value of sLOX-1=165.34 pg/ml were 80% and 70%, respectively. As for hs-CRP, the AUC was 1.0, 95%CI=1.0–1.0, $p<0.001$. The sensitivity and specificity of the test at a cut-off value of hs-CRP=11.13 mg/L was 100% for each.

For sLOX-1/OX-LDL ratio, the AUC was 0.841, 95%CI=0.735–0.947, $p<0.001$. The sensitivity and specificity of the test at cut off value of sLOX-1/OX-LDL ratio=32.76 mg/L was 77% and 87%, respectively (Fig. 3).

Correlations between Different Variables

Spearman correlation was used to explore the possible correlations between markers and other continuous variables in each group.

In this group, sLOX-1 displayed a significant correlation with each of LDL (r=0.356, $p=0.05$) (Table 4).

DISCUSSION

High levels of sLOX-1 may be a promising biomarker for atherosclerotic plaque vulnerability.

In addition to plaque rupture, lox-1 plays an essential role in plaque formation (Kume *et al.*, 2010; Misaka *et al.*, 2014). LDL is oxidatively transformed when it reaches the vascular wall and becomes embedded in the extracellular matrix, resulting in ox-LDL. Inflammatory cells absorb the oxLDL to reduce lesions and apparent excessive lipid accumulation. This process is thought to play a role in the onset and development of the disease since it can contribute to the formation of fragile plaque, which can rupture (Markstad *et al.*, 2019). Extracellular aggregation of lipoprotein-derived lipids, death of reparative cells in the plaque, and MMPs degradation of fibrous tissue all occur before plaque breakup, resulting in fragile plaques with inflammation and a thin fibrous cap covering a necrotic core (Ornello *et al.*, 2018). The result of the study was in agreement with (Barreto *et al.*, 2020). sLox-1 levels are higher in ST-segment–elevation myocardial infarction patients than in non–ST-segment–elevation myocardial infarction patients peaking earlier than troponin. Further experiments demonstrating timely elevation of sLox-1 in patients with ACS corroborated these results. These findings support the contention that measurement of sLOX-1 can be used to improve diagnostic precision in the early diagnosis and characterization of ACS patients.

The sensitivity and specificity of the sLOX-1 were calculated and represented on a ROC curve. The AUC value between samples of unstable angina and the control samples was 0.81. In contrast, sensitivity was at 83% and specificity at 87%. It gives an idea of the strength of the biomarker. On the other hand, the AUC value between the myocardial infarction and control samples was 0.85. This value also showed that the biomarker is good for ACS cases (Kook *et al.*, 2020).

Table 4. Spearman correlation between different markers and other parameters in UA group

Variables	sLox-1	OX-LDL	hs-CRP
Age			
r	–0.230	–0.079	0.162
p	0.221	0.677	0.394
TC			
r	0.341	–0.050	0.073
p	0.065	0.795	0.700
TG			
r	0.088	–0.040	0.173
p	0.644	0.833	0.359
HDL			
r	–0.065	0.062	–0.049
p	0.731	0.747	0.796
LDL			
r	0.356	–0.056	0.036
p	0.05	0.770	0.852
VLDL			
r	0.058	–0.063	0.272
p	0.761	0.742	0.146
sLOX-1			
r			
p			
OX-LDL			
r	0.001		
p	0.997		
Hs-CRP			
r	0.063	–0.249	
p	0.743	0.184	

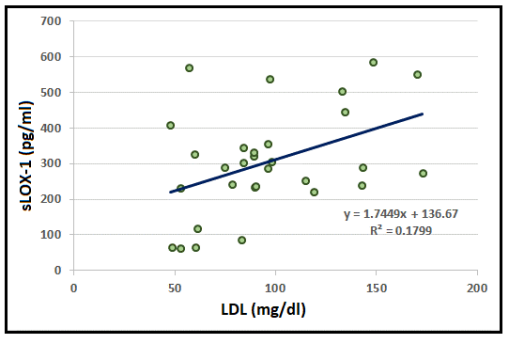

Figure 4. Regression analysis between LDL and sLOX-1 in UA group

sLOX-1 displayed a significant correlation with LDL and Myoglobin (r=0.356, p=0.05) for each other.

On the other hand, in our study, the ox-LDL result was not significant. The lectin-like oxidized low-density lipoprotein receptor 1 (LOX1) was discovered as the ox-LDL receptor on endothelial cells in 1998 (Civelek *et al.*, 2015). LOX-1 expression is very low at normal conditions, and ox-LDL induces endothelial LOX-1 upregulation in proatherogenic conditions (Yokota *et al.*, 2016). The ratio calculated between sLOX-1 and ox-LDL was highly significant in myocardial infarction compared with unstable angina and control samples. A ROC curve was worked out between samples of myocardial infarction and unstable angina to find out the sensitivity and specificity of AUC. The sensitivity and specificity were at 0.71. Thus, the sensitivity value was good, but the specificity value was poor. Compared with the ROC curve between the myocardial infarction and control samples, the AUC was at 0.84, so this group's sensitivity and specificity values were more substantial.

Our results agreed with previous work stating that troponin's value correlated with myocardial infarction (Möckel *et al.*, 2015). As a result of its ability to be released following myocardial cell injury, it has been adopted as a favored biomarker to identify acute coronary syndrome (ACS) (Sedighi *et al.*, 2020). On another side, it resulted in hs-CRP significant elevation because inflammation plays a vital role in atherosclerosis. Hepatocytes produce hs-CRP, which interleukin-6 primarily regulates as an inflammatory marker (IL-6). According to growing research, hs-CRP appears to be a helpful prognostic factor for individuals with cardiac disease (Wang *et al.*, 2019; Dogdu, 2020). In this study, lipid profile results have a non-significant elevation, except the high-density lipoprotein due to taking medications, fasting period before collection of the sample, or other causes.

As LOX-1 is a membrane-bound protein with a single C-terminal domain, the main novelty of the present work can be cleaved and released as a soluble form in the circulation, thus allowing its measurement in patients. sLOX-1 increases in plasma or serum of patients with ACS or CAD compared to control subjects and when combined with other serum biomarker levels might potentially increase the diagnostic accuracy of acute coronary syndromes or predict disease progression or the risk of future cardiovascular events.

The present study has several limitations. First, changes in sLOX-1 levels before and after the onset of the attack have not been examined because this is a case-control study. Second, variation in sLOX-1 levels could be significant, and the power to estimate the differences may not be adequate because of the small sample size. Further examinations with a largea number of cases are required to clarify the role of sLOX-1 in each type of ACS. Third, delay in blood sampling in the present study could underestimate the levels of sLOX-1 because peak levels of sLOX-1 in acute coronary syndrome were reported within one day after admission.

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