NO	Title	Journal, Volume	Author(s)	Publication date	Abstract
1	LOX Index, a Novel Predictive Biochemical Marker for Coronary Heart Disease and Stroke	Clinical Chemistry 56:4 550–558(2010)	Nobutaka Inoue	2010/1/21	**BACKGROUND**: Lectin-like oxidized LDL receptor 1 (LOX-1) is implicated in atherothrombotic diseases. Activation of LOX-1 in humans can be evaluated by use of the LOX index, obtained by multiplying the circulating concentration of LOX-1 ligands containing apolipoprotein B (LAB) times that of the soluble form of LOX-1 (sLOX-1) [LOX index LAB sLOX-1]. This study aimed to establish the prognostic value of the LOX index for coronary heart disease (CHD) and stroke in a community-based cohort. **METHODS**: An 11-year cohort study of 2437 residents age 30–79 years was performed in an urban area located in Japan. Of these, we included in the analysis 1094 men and 1201 women without history of stroke and CHD. We measured LAB and sLOX-1 using ELISAs with recombinant LOX-1 and monoclonal anti-apolipoprotein B antibody and with 2 monoclonal antibodies against LOX-1, respectively. **RESULTS**: During the follow-up period, there were 68 incident cases of CHD and 91 cases of stroke (with 60 ischemic strokes). Compared with the bottom quartile, the hazard ratio (HR) of the top quartile of LOX index was 1.74 (95% CI 0.92–3.30) for stroke and 2.09 (1.00–4.35) for CHD after adjusting for sex, age, body mass index, drinking, smoking, hypertension, diabetes, non-HDL cholesterol, and use of lipid-lowering agents. Compared with the bottom quartile of LOX index, the fully adjusted HRs for ischemic stroke were consistently high from the second to the top quartile: 3.39 (95% CI 1.34–8.53), 3.15 (1.22– 8.13) and 3.23 (1.24–8.37), respectively. **CONCLUSIONS**: Higher LOX index values were associated with an increased risk of CHD. Low LOX index values may be protective against ischemic stroke.
2	The Relationship between Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1 Ligands Containing Apolipoprotein B and the Cardio-Ankle Vascular Index in Healthy Community Inhabitants: The KOBE Study	Journal of atherosclerosis and thrombosisJ Atheroscler Thromb. 2014 Nov 6.	Daisuke Sugiyama	2014/11/6	**METHODS:** The participants were 515 healthy Japanese (310 men and 205 women) without a history of CVD, cancer or the use of medication for hypertension, diabetes or dyslipidaemia. To estimate the association between LOX-1-related modified LDL indicators (LAB, soluble form of LOX-1 (sLOX-1)) and the CAVI, we performed multivariable linear regression analyses with possible confounders such as the serum LDL cholesterol level. **RESULTS:** The plasma LAB showed a positive association with the CAVI in men (standardized coefficient: 0.11, p = 0.04). This relationship was not observed in women. On the other hand, no clear association was observed between the CAVI and the plasma sLOX-1 level in either sex. **CONCLUSIONS:** The plasma LAB levels may represent a useful marker for detecting potential atherosclerosis in healthy individuals considered to be at low risk for atherosclerosis and CVD. Further studies are needed to confirm the present findings.
3	Soluble lectin-like oxidized LDL receptor-1 (sLOX-1) as a sensitive and specific biomarker for acute coronary syndrome——Comparison with other biomarkers	Journal of Cardiology (2010) 56, 159—165	Noriaki Kume	2010/6/1	**BACKGROUND:** Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) appears to be involved in atherosclerotic plaque vulnerability and rupture. Circulating soluble LOX-1 (sLOX-1) levels are dramatically elevated in patients with acute coronary syndrome (ACS), and its diagnostic sensitivity and specificity is superior to high-sensitivity C-reactive protein (hs-CRP). In this study, we have compared the diagnostic value of sLOX-1 for ACS with those of troponin T (TnT) and heart-type fatty acid binding protein (H-FABP). **METHODS:** One hundred and seven patients who underwent coronary angiography (CAG), including 18 ACS and 89 non-ACS patients were enrolled. Peripheral blood samples were obtained during the emergent or elective CAG. The non-ACS group consisted of 30 patients with normal CAG, 30 stable angina pectoris patients controlled by medical treatment, and 29 patients with stable angina who required elective coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft). **RESULTS:** Age, gender, lipid profiles, or prevalence of diabetes, smoking, or hypertension were not significantly different between ACS and non-ACS. These factors did not significantly affect blood sLOX-1 levels. Circulating sLOX-1, TnT, and H-FABP levels were significantly higher in ACS than non-ACS. Area under the curve (AUC) values of the receiver-operating characteristic curves were 0.948, 0.704, and 0.691 for sLOX-1, TnT, and H-FABP, respectively. In a TnT-negative (<0.03 ng/mL) subgroup, the AUC values for sLOX-1 and H-FABP were 0.848 and 0.476, respectively. **CONCLUSION:** Circulating sLOX-1 is a more sensitive and specific biomarker for ACS than TnT and H-FABP, and provides additional diagnostic values when measured in combination with TnT.

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4	Associations of atherosclerotic risk factors with oxidized low-density lipoprotein evaluated by LOX-1 ligand activity in healthy men	Clinical Chimica Acta 412 (2011) 1643-1647	Kagehiro Uchida	2011/5/23	**Background:** The aim of this study was to determine the relationships of risk factors for atherosclerosis with oxidized low-density lipoprotein (OxLDL) evaluated by a new enzyme immunoassay for measurement of LOX-1 (lectin-like OxLDL receptor) ligand. **Methods**: Subjects were 236 healthy men aged 33-62 years. LOX-1 ligand containing apoB (LAB) was measured by an enzyme-immunoassay using immobilized recombinant LOX-1 and anti-ApoB monoclonal antibody. **Results:** In simple regression analysis, log-converted LAB showed significant positive correlations with history of smoking, waist circumference, diastolic blood pressure, LDL cholesterol, log-converted triglycerides, uric acid and white blood cell count and showed a significant negative correlation with HDL cholesterol. In multiple regression analysis using history of smoking, history of drinking, waist circumference, diastolic blood pressure, HDL cholesterol, log-converted triglycerides and uric acid as explanatory variables, log-converted LAB showed significant correlations only with history of smoking and log-converted triglycerides. Log-converted LAB was significantly higher in heavy smokers (≥ 20 cigarettes per day) than in nonsmokers and light smokers (< 20 cigarettes per day), while no difference in log-converted LAB was found between nonsmokers and light smokers. Log-converted LAB was significantly higher in subjects with hypertriglyceridemia (≥ 150 mg/dl), large waist circumference (≥ 85 cm), high diastolic blood pressure (≥ 85 mm Hg), or metabolic syndrome defined by the NCEP-ATP III criteria than in subjects without each risk factor or metabolic syndrome. **Conclusions:** Hypertriglyceridemia and smoking are determinants of LOX-1 ligand activity in healthy men and are thus thought to be crucial risk factors for initiation of atherosclerotic progression through generation of OxLDL.
5	C-reactive protein enhances LOX-1 expression in human aortic endothelial cells: relevance of LOX-1 to C-reactive protein-induced endothelial dysfunction.	Circulation Reserch 2004;95:877-883	Ling Li	2004/9/28	C-reactive protein (CRP), a characteristic inflammatory marker, is a powerful predictor of cardiovascular events. Recent data suggest that CRP may also promote atherogenesis through inducing endothelial dysfunction. Lectin-like oxidized low-density lipoprotein (oxLDL) receptor-1 (LOX-1) is a newly identified endothelial receptor for oxLDL that plays a pivotal role in oxLDL-induced endothelial dysfunction. Whether CRP may regulate endothelial LOX-1 and induce endothelial dysfunction through this receptor is unknown. In the present study, we studied the in vitro effect of CRP on LOX-1 expression in human aortic endothelial cells (HAECs) and the role of LOX-1 in CRP-induced human monocyte adhesion to endothelium and oxLDL uptake by endothelial cells. Incubation of HAECs with CRP enhanced, in a dose- and time-dependent manner, LOX-1 mRNA and protein levels. Induction of LOX-1 protein was already present at 5 microg/mL CRP and reached a maximum at 25 microg/mL. This effect was reduced by antibodies against CD32/CD64, endothelin-1 (ET-1) and interleukin-6 (IL-6). The extent of stimulation of LOX-1 achieved by CRP was comparable to that elicited by high glucose and IL-6 and remained unchanged in presence of these factors. Finally, CRP increased, through LOX-1, both human monocyte adhesion to endothelial cells and oxLDL uptake by these cells. We conclude that CRP enhances endothelial LOX-1 expression and propose a new mechanism by which CRP may promote endothelial dysfunction, that of inducing LOX-1.
6	LOX-1 ligands containing apolipoprotein B and carotid intima-media thickness in middle-aged community-dwelling US Caucasian and Japanese men	Atherosclerosis. 2013 Jul; 229(1): 240-245.	Tomonori Okamura	2013/4/30	**Objective:** The serum level of LOX-1 ligand containing ApoB (LAB) may reflect atherogenicity better than LDL cholesterol (LDLC), total LDL particles and usual measurement of oxidized LDL. The association between LAB and intima-media thickness (IMT) of carotid artery was investigated by ultrasound in US and Japan men. **Methods:** Participants were 297 US Caucasian and 310 Japanese men, aged 40 to 49 years without past history of cardiovascular disease. Serum LAB levels were measured by ELISAs with recombinant LOX-1 and monoclonal anti-apolipoprotein B antibody. **Results:** Serum LAB levels [median (interquartile range), μg/L] were 1,321 (936, 1730) in US Caucasians and 940 (688, 1259) in Japanese. For Caucasian men, average IMT was higher in higher LAB quartile, which was 0.653, 0.667, 0.688, and 0.702 mm, respectively (p for trend= 0.02). Linear regression analysis showed serum LAB was significantly associated with IMT after adjustment for LDLC or total LDL particles in addition to other traditional or novel risk factors for atherosclerosis such as C-reactive protein. However, there was no significant relationship between LAB and IMT in Japanese men. **Conclusion:** Serum LAB, a new candidate biomarker for residual risk, was associated with an increased carotid IMT in US Caucasian men independently of various risk factors; however, ethnic difference should be clarified in the future.
7	Correlation between pulse wave velocity and serum sLOX-1 in patients with acute cerebral infarction	Scientific Research and Essays Vol.6(31),pp6515-6519,December,2011	Chao Lai	2011/8/24	To investigate the relationship between pulse wave velocity (PWV) and serum lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1) level in patients with acute cerebral infarction, a total of 58 patients with acute cerebral infarction occurring within 72 h and 30 subjects (control) without stroke receiving physical examination were recruited into the present study. The right carotid-femoral PWV (cfPWV) was measured and serum sLOX-1 level was determined by ELISA. The PWV and serum sLOX-1 level in patients with acute cerebral infarction were significantly higher than those in the control group (PWV: 11.69 ± 2.56 m/s Vs. 9.60 ± 1.92 m/s, $P < 0.05$; sLOX-1: 42.92 ± 6.88 mg/L Vs. 36.03 ± 4.70 mg/L, $P < 0.01$). No marked difference was observed in the PWV and serum sLOX-1 level among patients with different infarction sizes. Correlation analysis revealed PWV was positively correlated with the serum sLOX-1 level ($r = 0.579$, $P < 0.01$). PWV has favorable consistence with sLOX-1 used as a non-invasive method to evaluate the degree of atherosclerosis in patients with acute cerebral infarction. PWV and sLOX-1 may have important clinical implications in the prevention and treatment of cerebral infarction.

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8	Plasma Soluble Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1 as a Novel Prognostic Biomarker in Patients With ST-Segment Elevation Acute Myocardial Infarction	Circulation Journal Vol.79, March 2015	Takumi Higuma	2015/1/23	**Background:** Soluble lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1) level is a reliable prognostic biomarker in acute coronary syndrome. However, it is unclear whether its plasma level at acute phase is related to the long-term prognosis in patients with ST-segment elevation acute myocardial infarction (STEMI). **Methods and Results:** We prospectively examined the relation between plasma sLOX-1 level on admission and prognosis in 153 consecutive STEMI patients admitted within 24 h of onset. Primary percutaneous coronary intervention was performed in 144 patients. The patients were divided into 2 groups by the median value (71 pg/ml) of plasma sLOX-1 level on admission [sLOX-1 level ≤71 pg/ml (n=77) and >71 pg/ml (n=76)], and were followed for median of 1,156 days. All-cause mortality and the combined endpoints of major adverse cardiovascular events (MACE) defined as cardiovascular mortality and recurrent MI were both significantly higher in patients with sLOX-1 values above median than in those below median (25.0% vs. 3.9%, P<0.001, and 19.4% vs. 6.5%, P=0.019 by log-rank test, respectively). Even after adjustment for confounders, a level of sLOX-1 above median was an independent predictor for all-cause mortality (hazard ratio (HR): 5.893; 95% confidence interval (CI): 1.665-20.854, P=0.006) and MACE (HR: 3.457; 95% CI: 1.164-10.270, P=0.030). **Conclusions:** Elevated plasma sLOX-1 level on admission independently predicts long-term all-cause mortality and MACE after STEMI.
9	LOX-1 is a novel marker for peripheral artery disease in patients with type 2 diabetes	Metabolism Clinical and experimental 62(2013) 935-938	Michiaki Fukui	2013/2/21	**Objective:** The aim of this study was to investigate whether serum soluble lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1), which mediates initiation and progression of atherosclerosis in endothelial cells, could be a novel marker for peripheral artery disease (PAD) in patients with type 2 diabetes. **Methods:** We evaluated relationships of serum sLOX-1 to ankle-brachial index (ABI) and examined the association of serum sLOX-1 with PAD in 410 patients with type 2 diabetes. **Results:** Serum sLOX-1 was inversely correlated with ABI (r=−0.197, P<0.0001). Stepwise regression analysis demonstrated that serum sLOX-1 (β =−0.168, F=5.571, P<0.05) was independently associated with ABI, and multiple logistic regression analysis demonstrated that serumsLOX-1 (16.254 (1.237-213.651), P=0.0339) was independently associated with PAD. **Conclusions:** Serum sLOX-1 is associated with ABI and it could be a novel marker for PAD in patients with type 2 diabetes.
10	Lectine-Like Oxidized Low-Density Lipoprotein Receptor-1 Plays an Important Role in Vascular Inframmation in Current Smokers.	Journal of atherosclerosis and thrombosis Vol.20, No.6	Rieko Takanabe-Mori	2013/2/7	**AIM:** Smoking induces vascular inflammation and increases the risk of cardiovascular events. Lectinlike oxidized low-density lipoprotein receptor-1 (LOX-1) is a scavenger receptor that is induced by oxidative stress and is associated with atherosclerotic plaque formation and destabilization. LOX-1 interacts with C-reactive protein (CRP) and plays an important role in inflammatory diseases. We therefore hypothesized that LOX-1 may be involved in the onset of smoking-induced vascular inflammation. **METHODS:** We measured the soluble LOX-1 (sLOX-1) levels in sera obtained from 207 current smokers. **RESULTS:** The serum sLOX-1 levels positively correlated with various smoking variables, such as the number of cigarettes smoked per day (r= 0.150, p<0.05), the expired air carbon monoxide (CO) concentrations (r= 0.198, p<0.005) and the Fagerstrom test for nicotine dependence scores (r= 0.190, p<0.01). The serum levels of sLOX-1 also correlated with those of a representative inflammatory marker, the serum high-sensitivity CRP level (hsCRP; r= 0.232, p<0.005). A multivariate regression analysis revealed the independent determinants of the serum sLOX-1 level to be the expired air CO concentration (β = 0.182, p<0.05) and the hsCRP level (β = 0.213, p<0.01). **CONCLUSIONS:** The serum sLOX-1 level was found to increase in close association with both the smoking-related variables and the inflammatory marker hsCRP. These findings suggest that LOX-1 may therefore play an important role in the onset of smoking-induced inflammation and atherosclerosis in humans.

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11	Caloric Restriction, Aerobic Exercise Training, and Soluble Lectin-like Oxidized LDL Receptor-1 Levels in Overweight and Obese Postmenopausal Women	Int J Obes (Lond). 2011 June ; 35(6): 793-799.	Tina E. Brinkley	2010/9/21	**BACKGROUND:** Elevated circulating levels of soluble lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1) have been observed in obese persons and are reduced by weight loss. However, it is not known whether combining caloric restriction (CR) with exercise training is better in reducing sLOX-1 levels than CR alone. **OBJECTIVE:** We examined whether the addition of aerobic exercise to a weight loss intervention differentially affects sLOX-1 levels in 61 abdominally obese post-menopausal women randomly assigned to a CR only (n = 22), CR+moderate-intensity exercise (n = 22) or CR+vigorous-intensity exercise (n = 17) intervention for 20 weeks. The caloric deficit was ~2800 kcal per week for all groups. **RESULTS:** The intervention groups were similar at baseline with respect to body weight, body composition, lipids and blood pressure. However, plasma sLOX-1 levels were higher in the CR-only group (99.90 ± 8.23 pg ml(-1)) compared with both the CR+moderate-intensity exercise (69.39 ± 8.23 pg ml(-1), P = 0.01) and the CR+vigorous-intensity exercise (72.83 ± 9.36 pg ml(-1), P = 0.03) groups. All three interventions significantly reduced body weight (~14%), body fat and waist and hip circumferences to a similar degree. These changes were accompanied by a 23% reduction in sLOX-1 levels overall (-19.00 ± 30.08 pg ml(-1), P < 0.0001), which did not differ among intervention groups (P = 0.13). Changes in body weight, body fat and maximal oxygen consumption (VO(2) max) were not correlated with changes in sLOX-1 levels. In multiple regression analyses in all women combined, baseline sLOX-1 levels (β = -0.70 ± 0.06, P < 0.0001), age (β = 0.92 ± 0.43, P = 0.03) and baseline body mass index (BMI) (β = 1.88 ± 0.66, P = 0.006) were independent predictors of the change in sLOX-1 with weight loss. **CONCLUSIONS:** Weight loss interventions of equal energy deficit have similar effects on sLOX-1 levels in overweight and obese post-menopausal women, with the addition of aerobic exercise having no added benefit when performed in conjunction with CR.
12	Pitavastatin reduces lectin-like oxidized low-density lipoprotein receptor-1 ligands in hypercholesterolemic humans	Lipids 45:329-335(2010)	Tetsuya Matsumoto.	2010/3/13	The aim of this study was to determine the impact of pitavastatin on low density lipoprotein cholesterol (LDL-C) and lectin-like oxidized LDL receptor-1 (LOX-1) in patients with hypercholesterolemia. Twenty-five hypercholesterolemic patients (8 male, 17 female; age 66 +/- 13, 21-80 years) who had not received anti-dyslipidemic agents and had LDL-C levels of more than 160 mg/dL were examined. Biochemical factors were measured at baseline and after treatment with pitavastatin (2 mg/day) for 6 months. Serum levels of LOX-1 with apolipoprotein B-100 particle ligand and a soluble form of LOX-1 (sLOX-1) were measured by ELISA. All subjects completed the study with no adverse side effects. Total-C (268 +/- 26 vs. 176 +/- 17 mg/dL), LDL-C (182 +/- 21 vs. 96 +/- 14 mg/dL), and LOX-1 ligand (867 +/- 452 vs. 435 +/- 262 ng/mL) were reduced with pitavastatin treatment (P < 0.0001 for each). Significant decreases in triacylglycerols were noted (P < 0.0001), but there were no changes in high-density lipoprotein cholesterol. After 6 months, there were no significant changes in high-sensitivity CRP or soluble LOX-1. At baseline, there were no significant correlations between LOX-1 ligand and either LDL-C or sLOX-1. The decrease in LOX-1 ligand was not correlated with the decrease in LDL-C, but was correlated with the decrease in sLOX-1 (r = 0.47, P < 0.05). In conclusion, pitavastatin therapy had beneficial effects on markers of oxidative stress in hypercholesterolemic subjects. Serum levels of LOX-1 ligand may be a useful biomarker of the pleiotropic effects of statins.
13	Circulating soluble lectin-like oxidized low-density lipoprotein receptor-1 levels are associated with angiographic coronary lesion complexity in patients with coronary artery disease	Clin. Cardiol. 34, 3, 172-177 (2011)	Zi-Wen Zhao	2010/11/11	**BACKGROUND:** Angiographic coronary lesion complexity has been reported to predict plaque vulnerability. It is important to develop a noninvasive blood biomarker for accurate prognostication of angiographically complex lesions in patients with coronary artery disease (CAD). **HYPOTHESIS:** Serum soluble lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1) levels may be correlated with coronary lesion complexity in patients with CAD. **METHODS:** We measured serum sLOX-1 levels in 180 consecutive patients undergoing coronary angiography for the evaluation of CAD. Coronary lesions were classified as simple or complex lesions based on coronary plaque morphology. **RESULTS:** Stable CAD patients with complex lesions (n=50) had significantly higher serum sLOX-1 levels than those with simple lesions (n=72), at 0.914 ng/mL (range, 0.489-1.296 ng/mL) vs 0.426 ng/mL (range, 0.195-1.075 ng/mL), respectively, P<0.01. Multivariate logistic regression analysis revealed that sLOX-1 levels were independently associated with the presence of complex lesions in patients with stable CAD (odds ratio [OR]: 1.964, 95% confidence interval [CI]: 1.149-3.356, P<0.05). Among patients with acute coronary syndrome (n=58), who had significantly higher circulating sLOX-1 levels than stable CAD patients (n=122) at 1.610 ng/mL (range, 0.941-2.264 ng/mL) vs 0.579 ng/mL (range, 0.265-1.172 ng/mL), respectively, P<0.01, sLOX-1 levels were independently associated with the presence of multiple complex coronary lesions (OR: 1.967, 95% CI: 1.075-3.600, P < 0.05). **CONCLUSIONS:** Serum sLOX-1 levels were associated with complex lesions that might predict vulnerable plaques. This study suggested sLOX-1 might be a useful biomarker of coronary plaque vulnerability in patients with CAD.

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14	Increased serum soluble lectin-like oxidized low-density lipoprotein receptor-1 levels in patients with biopsy-proven nonalcoholic fatty liver disease	World J Gastroenterol. 2015 Jul 14;21(26):8096-102.	Ozturk O	2015/7/14	**AIM:**To analyze the relationship between the serum lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) levels and clinical and histopathological features of biopsy-confirmed nonalcoholic fatty liver disease (NAFLD) patients. **METHODS:**Fifty-three consecutive, biopsy-proven NAFLD patients (31 males and 22 females, mean age 42.5 ± 9.6 years) and 26 age- and gender-matched, healthy controls (14 males and 12 females, mean age 39 ± 10.7 years) were included. The patients with NAFLD were consecutive patients who had been admitted to the hepatology outpatient clinic within the last year and had been diagnosed with NAFLD as the result of liver biopsy. The healthy controls were individuals who attended the outpatient clinic for routine health control and had no known chronic illnesses. The histological evaluation was conducted according to the NAFLD activity scoring system recommended by The National Institute of Diabetes and Digestive and Kidney Diseases Nonalcoholic Steatohepatitis Clinical Research Network. The serum LOX-1 levels were measured using an ELISA kit (Life Science Inc. USCN. Wuhan, Catalog No. E1859Hu) in both patients and healthy controls. A receiver operating characteristic (ROC) curve analysis was used to identify the optimal cutoff value of LOX-1 and thereby distinguish between patients with nonalcoholic steatohepatitis (NASH) and healthy controls. A P-value < 0.05 was considered statistically significant. **RESULTS:** NAFLD and healthy control groups were similar in terms of age and sex. NAFLD patients consisted of 8 patients with simple steatosis (15%), 27 with borderline NASH (51%) and 18 with definitive NASH (34%). Metabolic syndrome was found in 62.2% of the patients with NAFLD. The mean serum LOX-1 level in biopsy-proven NAFLD patients was 8.49 ± 6.43 ng/mL compared to 4.08 ± 4.32 ng/mL in healthy controls (P = 0.001). The LOX-1 levels were significantly different between controls, simple steatosis and NASH (borderline+definite) cases (4.08 ± 4.32 ng/mL, 6.1 ± 6.16 ng/mL, 8.92 ± 6.45 ng/mL, respectively, P = 0.004). When the cut-off value for the serum LOX-1 level was set at 5.35 ng/mL, and a ROC curve analysis was performed to distinguish between steatohepatitis patients and controls; the sensitivity and specificity of the serum LOX-1 level were 69.8% and 69.2%, respectively. **CONCLUSION:** The serum LOX-1 levels were significantly higher in NAFLD patients than in healthy controls. Additionally, the serum LOX-1 levels could differentiate between steatohepatitis patients and healthy controls.
15	High Levels of Soluble Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1 in Acute Stroke: An Age- and Sex-Matched Cross-Sectional Study	J Atheroscler Thromb, 2016; 23.	Chiaki Yokota	2010/9/21	**Aim:** Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is known to be a key molecule in the pathogenesis of atherosclerosis. Although high levels of serum soluble LOX-1 (sLOX-1) were demonstrated in patients with acute coronary syndrome, there are no reports about acute stroke patients. The aim of the present study was to evaluate the levels of sLOX-1 in acute stroke patients according to different stroke subtypes. **Methods:** We enrolled a total of 377 patients with a stroke (men/women: 251/126; age: 40-79 years), 250 with ischemic stroke and 127 with intracerebral hemorrhage (ICH). Patients were admitted to our hospital within 3 days after the onset of stroke. As controls, we randomly selected age- and sex-matched subjects without a past history of cardiovascular disease according to stroke subtype from the community-based cohort of the Suita study. Serum LOX-1 levels were compared between stroke patients and healthy controls according to stroke subtype. **Results:** Median values of serum sLOX-1 in stroke patients were significantly higher than those in controls (526 vs. 486 ng/L in ischemic stroke and 720 vs. 513 ng/L in ICH, respectively). Among subtypes of ischemic stroke, median sLOX-1 levels in atherothrombotic brain infarction (641 ng/L) only were significantly higher than those in controls (496 ng/L). Ischemic stroke [odds ratio (OR), 3.80; 95% confidence interval (CI), 1.86-7.74] and ICH (OR, 5.97; 95% CI, 2.13-16.77) were independently associated with high levels of sLOX-1 by multivariate logistic regression analysis. **Conclusions:** Higher levels of sLOX-1 were observed in patients with acute stoke than in controls. High levels of sLOX-1 can be useful as biomarker for acute stroke.
16	Cardiovascular risk assessment using LOX-index and Self-Rating Depression Scale	International Journal of Cardiology Metabolic & Endocrine	Nobutaka Inoue	2016/5/22	**Objective:** LOX-Index is a novel biomarker for cardiovascular disease (CVD) and is calculated by multiplying LOX-1 ligands containing apolipoprotein B (LAB) and soluble LOX-1 (sLOX-1). The Framingham risk score (FRS) is a common clinical tool for risk assessment of coronary artery disease. Mental stress can also be an important risk factor for CVD. The purpose of this study was to examine the relationship between LOX-Index and FRS or mental stress. **Methods:** LOX-Index was measured in 453 subjects including 150 consecutive outpatients with lifestyle-related diseases such as diabetes, hyperlipidemia, and hypertension and 303 healthy volunteers. Mental stress was evaluated by the Self-Rating Depression Scale (SDS). **Results:** LOX-Index was significantly related with the 10-years risk of FRS. Multiple regression analysis demonstrated that LAB was closely associated with the smoking status, low-density lipoprotein (LDL), and high-density lipoprotein (HDL). There were no significant associations between LOX-Index and the SDS scores; however, by simultaneously using LOX-Index and SDS, the subjects could be classified in terms of oxidative stress and mental stress. **Conclusions:** LOX-Index appears to be a comprehensive marker that could evaluate the status of multiple CVD risk factors. The classification with LOX-Index and SDS could contribute to the risk assessment for CVD.

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17	Serum level of LOX-1 ligand containing ApoB is associated with increased carotid intima-media thickness in Japanese community-dwelling men, especially those with hypercholesterolemia LOX-1 ligand and IMT in Japanese	Journal of Clinical Lipidology (2016) 10, 172-180	Tomonori Okamura	2015/10/26	**BACKGROUND:** The serum level of LOX-1 ligand containing ApoB (LAB) may reflect atherogenicity better than usual lipid parameters; however, the relationship between LAB and carotid intima-media thickness (IMT) was not clear even in Asian populations. **METHODS:** A total of 992 community-dwelling Japanese men, aged 40 to 79 years, were enrolled in the present study. Serum LAB levels were measured by enzyme-linked immunosorbent assays (ELISAs) with recombinant LOX-1 and monoclonal anti-apolipoprotein B antibody. **RESULTS:** Serum LAB levels (median [interquartile range], μg cs/L) were 5341 μg cs/L (4093-7125). The mean average IMT of the common carotid artery was highest in the fourth LAB quartile (842 μm) compared with the first quartile (797 μm) after adjustment for age, high-density lipoprotein cholesterol, triglyceride, body mass index, hypertension, diabetes, high sensitivity C-reactive protein, smoking, and alcohol drinking. However, this statistically significant difference was lost after further adjustment for total cholesterol (TC). After stratification using the combination of median LAB and hypercholesterolemia (serum TC ≥ 6.21 mmol/L and/or lipid-lowering medication), the adjusted mean average IMT (standard error) in the high LAB/hypercholesterolemia group was 886 μm (12.7), 856 μm (16.7) in the low LAB/hypercholesterolemia group, and 833 μm (8.4) in the low LAB/normal cholesterol group (P = .004). After further adjustment for TC, mean average IMT in the high LAB group was significantly higher than that measured in the low LAB group in hypercholesterolemic participants not taking lipid-lowering medication. **CONCLUSION:** Serum LAB was associated with an increased carotid IMT in Japanese men, especially those with hypercholesterolemia.
18	Association between plasma sLOX-1 concentration and arterial stiffness I n middle-aged and older indiviuduals	J. Clin. Biochem. Nutr. | September 2015 | vol. 57 | no. 2 | 151-155	Takeshi Otsuki	2015/9/15	Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is implicated in vascular endothelial function. Vascular endothelial function is a potent regulator of arterial stiffness, an independent risk factor for cardiovascular disease. However, it is unknown whether LOX-1 is associated with arterial stiffness. Plasma concentrations of soluble LOX-1 (sLOX-1) and brachial-ankle pulse wave velocity (baPWV, an index of arterial stiffness) were measured in 143 individuals between 51 and 83 years of age. Plasma sLOX-1 concentration was correlated with baPWV (r = 0.288, p = 0.0005). In stepwise regression analysis, plasma sLOX-1 concentration was associated with baPWV, after adjusting for age; body mass index; blood pressure; heart rate; blood levels of cholesterol, triglycerides, glucose, hemoglobin A1c, and insulin; sex; and use of antihypertensives, lipid-lowering agents, and other medications (R2 = 0.575, p<0.0001). Multiple logistic regression demonstrated that plasma sLOX-1 concentration was independently associated with elevated baPWV (≥14.0 m/s; odds ratio, 1.01; 95% confidence interval, 1.00-1.03; p = 0.03). These results suggest that LOX-1 is associated with arterial stiffness.
19	Smoking cessation reduces the lectin-like low-density lipoprotein receptor index, an independent cardiovascular risk marker of vascular inflammation	Heart Vessels,21 July 2017	Maki Komiyama	2017/7/21	Vessel wall inflammation promotes the destabilization of atherosclerotic plaques. The lectin-like oxidized low-density lipoprotein (LDL) receptor-1 (LOX-1) expressed by vascular cells and monocytes. LOX index is calculated by multiplying LOX-1 ligand containing apolipoprotein B level with the soluble LOX-1. A high LOX index reflects an increased risk for stroke and myocardial infarction. However, the change in LOX index after smoking cessation and the relationship between smoking-related variables and LOX index are unknown. Relation of the clinical parameters to the LOX index was examined on 180 subjects (135 males and 45 females) at the first visit to our outpatient clinic for smoking cessation. The impact of smoking cessation on the LOX index was also determined in the 94 subjects (62 males and 32 females) who successfully stopped smoking. Sex-adjusted regression analysis and multivariate analysis identified three independent determinants of the LOX index, namely, low-density lipoprotein-cholesterol (LDL-C; β = 0.311, $p < 0.001$), high-sensitivity C-reactive protein (β = 0.358, $p < 0.001$), and expired carbon monoxide concentration reflecting smoking heaviness (β = 0.264, p = 0.003). Body mass index (BMI) significantly increased 3 months after the onset of smoking cessation ($p < 0.001$). However, the LOX index significantly decreased ($p < 0.001$), regardless of the rate of increase in BMI post-cessation. The LOX index is closely associated with smoking heaviness as well as dyslipidemia and an inflammation marker. Smoking cessation may induce a decrease in this cardiovascular risk marker, independently of weight gain.
20	Stress Evaluation fro the Prevention of Karoshi (Mini Review)	Inoue, Occupational Medicine & Health Affairs 2016, 4:6	Nobutaka Inoue	2016/12/9	The pathophysiological effects of oxidized LDL are mainly mediated via the lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1). LOX-1 was identified as the receptor for oxidized LDL (oxLDL) on endothelial cells. LOX-1 expressed on the cell surface can be proteolytically cleaved by an undetermined enzymatic system in the membrane-proximal extracellular domain and released into the bloodstream as a soluble form. Recently, we reported the significance of LOX-index, which is calculated by multiplying the level of the LOX-1 ligands containing apo-lipoprotein B (LAB) and soluble LOX-1 (sLOX-1) as a predictive marker for stroke and cardiovascular disease. Data from the Suita cohort study revealed that a higher LOX-index was associated with an increased risk of cardiovascular diseases and stroke. It has been reported that the multivariable-adjusted hazard ratio for ischemic stroke and myocardial infarction from the second to top quartile of LOX-index was three-fold and two-fold higher, respectively, than that for the bottom quartile after multivariable adjustment in a community-based cohort study . Thus, the LOX-index might be a novel predictive marker for these diseases from the standpoint of oxidative stress.

NO	Title	Journal, Volume	Author(s)	Publication date	Abstract
21	Serum sLOX-1 Levels Are Correlated with the Presence and Severity of Obstructive Sleep Apnea	Genet Test Mol Biomarkers. 2015 May 1; 19(5): 272-276.	Chun-Yan	2015/5/1	Inflammation plays a critical role in the development and progression of obstructive sleep apnea (OSA). Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) activation is involved in the pathophysiology of inflammatory process-related disorders. Objective: This study aims to investigate whether serum soluble LOX-1 (sLOX-1) levels are associated with the presence and severity of OSA. Materials and Methods: A total of 137 OSA patients and 78 controls were recruited in this study. Serum sLOX-1 levels were measured by enzyme-linked immunosorbent assay. The severity of OSA was assessed by the apnea-hypopnea index (AHI). Results: OSA patients had significantly higher serum sLOX-1 levels compared with controls. Serum sLOX-1 levels elevated with the increment of OSA severity. sLOX-1 was the independent predictor of OSA. Serum sLOX-1 levels were significantly correlated with AHI and high-sensitivity C-reactive protein levels. Conclusions: Serum sLOX-1 levels were independently correlated with the presence and severity of OSA. These findings revealed that sLOX-1 might function as a potential biomarker for monitoring the development and progression of OSA.
22	Weight reduction can decrease circulating soluble lectin-like oxidized low-density lipoprotein receptor-1 levels in overweight middle-aged men	Metabolism. 2009 Sep;58(9):1209-14.	Nomata Yasuhiro	2009/9/1	Circulating soluble lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1) has been reported to be associated with acute coronary syndrome, but its association with obesity has not been elucidated. In this study, we examined whether weight reduction would reduce the serum levels of sLOX-1 in a 12-week weight reduction intervention. Thirty-eight overweight middle-aged men were enrolled in the study, and 32 completed the intervention. The serum level of sLOX-1 was measured using a chemiluminescent enzyme-linked immunoassay. After the intervention program, body weight and the serum level of sLOX-1 decreased significantly (-7.5% +/- 4.8% and -72.1% +/- 35.9%, respectively). Changes in serum levels of sLOX-1 were positively correlated with changes in body weight (r = 0.54, P = .003), body mass index (r = 0.57, P = .001), body fat mass (r = 0.57, P = .002), total cholesterol (r = 0.41, P = .03), subcutaneous fat area (r = 0.50, P = .007), high-sensitivity C-reactive protein (r = 0.56, P = .002), leptin (r = 0.47, P = .01), and tumor necrosis factor-alpha (r = 0.32, P = .09); but no correlations were observed with fasting glycemic-related factors (blood glucose, hemoglobin A(1c), and insulin). Changes in body mass index and high-sensitivity C-reactive protein were selected as significant predictors of sLOX-1 changes by multiple regression analyses. These results suggest that LOX-1 induction may be related to adipocyte metabolism, inflammation, and immune response associated with obesity
23	Serum Lectin-Like Oxidized-Low Density Lipoprotein Receptor-1 and Adiponectin Levels Are Associated With Coronary Artery Disease Accompanied With Metabolic Syndrome	Iran Red Crescent Med J. 2014 Aug;16(8):e12106.	Md Sayed AS	2014/8/5	**Background:** Coronary artery disease (CAD) is a major public health problem for developed and developing countries and is the single leading cause of death worldwide. **Objectives:** There is very few evidence regarding changes of both serum Lectin-like oxidized-low density lipoprotein receptor-1 (LOX-1) and adiponectin in patients with CAD accompanied with metabolic syndrome (MS). Here we aimed to evaluate serum levels of LOX-1 and adiponectin in patients with CAD accompanied with MS. **Patients and Methods:** Thirty patients with coronary artery disease without metabolic syndrome, 30 patients with coronary artery disease and metabolic syndrome, 30 ones with metabolic syndrome and 30 healthy subjects were enrolled. For all subjects, a questionnaire was filled to collect data, and peripheral blood samples were collected aseptically from the antecubital vein to measure serum Lectin-like oxidized-low density lipoprotein receptor-1 and adiponectin levels by enzyme-linked immunosorbent assay. **Results:** Serum LOX-1 level was highest in CAD + MS group; the difference between control and disease groups was statistically significant ($P < 0.001$). Adiponectin level had the lowest value in CAD + MS group; the difference between control and disease groups was statistically significant ($P < 0.05$). No significant differences were observed in serum Lectin-like oxidized-low density lipoprotein receptor-1and adiponectin in patients with different ages and gender. Serum LOX-1 level was changed negatively and linearly ($R2 = 0.721$) correlated with adiponectin level in different groups. **Conclusions:** Patient with CAD and MS had higher risk than those with only CAD because of lipid and glucose metabolism abnormalities. Combination measurements of serum LOX-1 and adiponectin levels may be helpful to evaluate the severity of CAD together with MS.
24	Pregnancy followed by delivery may affect circulating soluble lectin-like oxidized low-density lipoprotein receptor-1 levels in women of reproductive age	Mediators of Inflammation Volume 2012	Mehmet Balin	2012/3/1	**BACKGROUND/OBJECTIVE:** It is known that menopause or lack of endogenous estrogen is a risk factor for endothelial dysfunction and CAD. Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is involved inmultiple phases of vascular dysfunction. The purpose of the current study was to determine the association between soluble LOX-1 (sLOX-1) and pregnancy followed by delivery in women of reproductive age. **MATERIALS/METHODS:** Sixty-eight subjects with pregnancy followed by delivery (group 1) and 57 subjects with nongravidity (group 2) were included in this study. Levels of sLOX-1 were measured in serum by EL SA. **RESULTS:** Plasma levels of sLOX-1 were significantly lower in Group 1 than Group 2 in women of reproductive age (0.52 ± 0.18 ng/mL and 0.78 ± 0.13, resp., $P < 0.001$). There were strong correlations between sLOX-1 levels and the number of gravida ($r = -0.645$, $P < 0.001$). The levels of sLOX-1 highly correlated with the number of parous ($r = -0.683$, $P < 0.001$). **CONCLUSION:** Our study demonstrated that serum sLOX-1 levels were associated with pregnancy followed by delivery that might predict endothelial dysfunction. We conclude that pregnancy followed by delivery may delay the beginning and progress of arteriosclerosis and its clinical manifestations in women of reproductive age.

NO	Title	Journal, Volume	Author(s)	Publication date	Abstract
25	A pilot study investigating the LOX index as a potential biomarker of endothelial function in pregnancy	Hypertension Research in Pregnancy vol 5 2017.	Kohei Fujita	2017/11/15	**Aim:** This study aimed to determine the normal range of the lectin-like oxidised LDL receptor (LOX) index during pregnancy and investigate whether the index can be used as a biomarker of maternal endothelial function. **Methods:** We conducted a prospective pilot study consisting of 12 pregnant women without obstetric or medical complications and eight non-pregnant women at Kyoto University Hospital between March 2011 and March 2012. Endothelial function was evaluated by the reactive hyperaemia index (RHI) using Endo-PAT2000 in early, mid-, and late gestation. Plasma levels of soluble LOX-1 (sLOX-1) and LOX-1 ligand containing apolipoprotein B (LAB) in each gestation period were measured by ELISA. The LOX index was obtained by multiplying plasma levels of LAB with those of sLOX-1. **Results:** The LOX index increased significantly as gestational age advanced. The LOX index, but not LAB or sLOX-1, was correlated with RHI in mid-gestation (R=0.3352, P=0.0486). **Conclusions:** The LOX index during mid-gestation may be a useful biomarker of maternal endothelial function.
26	Relationship between sd-LDL and LOX-1 receptor ; from "Small dense LDL enhances THP-1 macrophage foam cell formation."	Jounal of Artheroscrelosis and Thrombosis Vol.18, No.8	Mariko Tani	2011/3/8	**AIM:** Increased levels of small dense low-density lipoproteins (sd-LDL) have been reported more atherogenic compared to total low-density lipoprotein (LDL); however, no definitive experiments using macrophages have examined this concept in vitro. **METHOD AND RESULT:** In this study, we isolated fractions of total LDL (density 1.019-1.063 g/ml) and sd-LDL (density 1.044-1.063 g/ml) from the plasma of subjects with modest hypertriglycidemia. Oxidizabilty as assessed by copper-induced generation (1.6 μmol/L CuSO(4),12 h) of thiobarbituric acid reactive substances (TBARS) was significantly greater (7-fold higher, $p < 0.01$) for sd-LDL (4.3 ± 1.1 nmol/mg) than for total LDL (0.6 ± 0.2 nmol/mg) at the same cholesterol concentrations. Moreover, oxidized sd-LDL induced more lipid staining in macrophages than oxidized total LDL. When non-oxidized sd-LDL were incubated with THP1 macrophages, there was much greater lipid accumulation as assessed by oil red O staining, and more than a 2-fold increase ($p < 0.05$) in intracellular triglyceride content as compared to non-oxidized total LDL. Furthermore, non-oxidized sd-LDL in contrast to non-oxidized total LDL enhanced macrophage lectin-like oxidized LDL receptor-1 (LOX-1) protein expression and significantly LOX-1 mRNA levels (+158%, $p < 0.05$), with no effect on scavenger receptor A or CD36 gene expression. These effects of non-oxidized sd-LDL on LOX-1 gene expression were suppressed when Toll-like receptor 4 was inactivated either by RNAi or antibody. **CONCLUSION:** Our data indicate for the first time that sd-LDL is much more effective in promoting macrophage triglyceride accumulation and LOX-1 gene expression than total LDL.
27	Relationship between HDL and LOX-1; from "Mechanisms underlying adverse effects of HDL on eNOS-activating pathways in patients with coronary artery disease"	The Journal of Clical Investigation 2011;121(7):2693-2708.	Cardiology Belser	2011/July	Therapies that raise levels of HDL, which is thought to exert atheroprotective effects via effects on endothelium, are being examined for the treatment or prevention of coronary artery disease (CAD). However, the endothelial effects of HDL are highly heterogeneous, and the impact of HDL of patients with CAD on the activation of endothelial eNOS and eNOS-dependent pathways is unknown. Here we have demonstrated that, in contrast to HDL from healthy subjects, HDL from patients with stable CAD or an acute coronary syndrome (HDLCAD) does not have endothelial antiinflammatory effects and does not stimulate endothelial repair because it fails to induce endothelial NO production. Mechanistically, this was because HDLCAD activated endothelial lectin-like oxidized LDL receptor 1 (LOX-1), triggering endothelial PKCβ II activation, which in turn inhibited eNOS-activating pathways and eNOS-dependent NO production. We then identified reduced HDL-associated paraoxonase 1 (PON1) activity as one molecular mechanism leading to the generation of HDL with endothelial PKCβ II-activating properties, at least in part due to increased formation of malondialdehyde in HDL. Taken together, our data indicate that in patients with CAD, HDL gains endothelial LOX-1- and thereby PKCβ II-activating properties due to reduced HDL-associated PON1 activity, and that this leads to inhibition of eNOS-activation and the subsequent loss of the endothelial antiinflammatory and endothelial repair-stimulating effects of HDL.
28	The relationship between serum lectin-like oxidized LDL receptor-1 levels and systolic heart failure	Acta Cardiol 2016; 71(2): 185-190	Feyzullah BESLI	April, 2013	**OBJECTIVES:** Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) appears to be involved in atherosclerotic plaque vulnerability and rupture. In this study, we aimed to evaluate the utility of serum LOX-1 levels in the diagnosis and assessment of left ventricular systolic HF and LOX-1's relationship with serum pro-brain natriuretic peptide (NT-proBNP). **DESIGN AND SETTINGS:** This was a cross-sectional study of all eligible patients admitted to the department of cardiology of the University Hospital between July 2011 and April 2012. **METHODS:** Fifty-five patients with a diagnosis of systolic heart failure and 25 patients without systolic HF were enrolled in this study. Serum C-reactive protein, NT-proBNP, and LOX-1 were studied. **RESULTS:** Serum LOX-1 and NT-proBNP levels were significantly higher in the heart failure group and showed a positive correlation with NT-proBNP and negative correlations with left ventricular ejection fraction (EF). In addition, LOX-1 levels in patients with ischaemic cardiomyopathy were significantly higher, while they were similar in patients with dilated cardiomyopathy compared to control subjects. **CONCLUSION:** Our study demonstrates the utility of the serum LOX-1 levels in the diagnosis of left ventricular systolic heart failure. LOX-1 may have a place in the diagnosis of heart failure, in particular in patients with ischaemic cardiomyopathy.

NO	Title	Journal, Volume	Author(s)	Publication date	Abstract
29	Bergamot polyphenolic fraction enhances rosuvastatin-induced effect on LDL-cholesterol, LOX-1 expression and protein kinase B phosphorylation in patients with hyperlipidemia	International Journal of Cardiology 170 (2013) 140–145	Micaela Gliozzi, Vincenzo Mollace	April, 2015	**BACKGROUND:**Statins are the most commonly prescribed drugs to reduce cardiometabolic risk. Besides the well-known efficacy of such compounds in both preventing and treating cardiometabolic disorders, some patients experience statin-induced side effects. We hypothesize that the use of natural bergamot-derived polyphenols may allow patients undergoing statin treatment to reduce effective doses while achieving target lipid values. The aim of the present study is to investigate the occurrence of an enhanced effect of bergamot-derived polyphenolic fraction (BPF) on rosuvastatin-induced hypolipidemic and vasoprotective response in patients with mixed hyperlipidemia. **METHODS:**A prospective, open-label, parallel group, placebo-controlled study on 77 patients with elevated serum LDL-C and triglycerides was designed. Patients were randomly assigned to a control group receiving placebo (n=15), two groups receiving orally administered rosuvastatin (10 and 20mg/daily for 30 days; n=16 for each group), a group receiving BPF alone orally (1000 mg/daily for 30 days; n=15) and a group receiving BPF (1000 mg/daily given orally) plus rosuvastatin (10mg/daily for 30 days; n=15). **RESULTS:**Both doses of rosuvastatin and BPF reduced total cholesterol, LDL-C, the LDL-C/HDL-C ratio and urinary mevalonate in hyperlipidemic patients, compared to control group. The cholesterol lowering effect was accompanied by reductions of malondialdehyde, oxyLDL receptor LOX-1 and phosphoPKB, which are all biomarkers of oxidative vascular damage, in peripheral polymorphonuclear cells. **CONCLUSIONS:**Addition of BPF to rosuvastatin significantly enhanced rosuvastatin-induced effect on serum lipemic profile compared to rosuvastatin alone. This lipid-lowering effect was associated with significant reductions of biomarkers used for detecting oxidative vascular damage, suggesting a multi-action enhanced potential for BPF in patients on statin therapy.
30	Association of Scavenger Receptors in Adipose Tissue With Insulin Resistance in Nondiabetic Humans	Arterioscler Thromb Vasc Biol. 2009 September; 29(9): 1328–1335.	Neda Rasouli, Philip A. Kern	September, 2009	**OBJECTIVE:**Scavenger receptors play crucial roles in the pathogenesis of atherosclerosis, but their role in insulin resistance has not been explored. We hypothesized that scavenger receptors are present in human adipose tissue resident macrophages, and their gene expression is regulated by adiponectin and thaizolidinediones. **METHODS AND RESULTS:**The gene expression of scavenger receptors including scavenger receptor-A (SRA), CD36, and lectin-like oxidized LDL receptor-1 (LOX-1) were studied in subcutaneous adipose tissue of nondiabetic subjects and in vitro. Adipose tissue SRA expression was independently associated with insulin resistance. Pioglitazone downregulated SRA gene expression in adipose tissue of subjects with impaired glucose tolerance and decreased LOX-1 mRNA in vitro. Macrophage LOX-1 expression was decreased when macrophages were cocultured with adipocytes or when exposed to adipocyte conditioned medium. Adding adiponectin neutralizing antibody resulted in a 2-fold increase in LOX-1 gene expression demonstrating that adiponectin regulates LOX-1 expression. **CONCLUSIONS:**Adipose tissue scavenger receptors are strongly associated with insulin resistance. Pioglitazone and adiponectin regulate gene expression of SRA and LOX-1, and this may have clinical implications in arresting the untoward sequalae of insulin resistance and diabetes, including accelerated atherosclerosis.
31	Lectic-like Oxidized Low-Density Lipoprotein Recptor 1 Signals Is a Potent Biomarker and Therapeutic Target for Human Rheumatoid Arthritis	ARTHRITIS & RHEUMATISM Vol.64, No.4, April 2012, pp 1024–1034	Masahiro ishikawa, Takahashi Nakamura	2012/4/1	**OBJECTIVE:** To determine whether lectin-like oxidized low-density lipoprotein (ox-LDL) receptor 1 (LOX-1) and the soluble form of LOX-1 (sLOX-1) are novel target molecules for the diagnosis and treatment of rheumatoid arthritis (RA). **METHODS:** Expression of ox-LDL and LOX-1 proteins in human RA synovium was evaluated by immunohistochemistry. Human RA fibroblast-like synoviocytes (FLS) were assessed for ox-LDL-induced expression of LOX-1 and ox-LDL-induced production of matrix metalloproteinase 1 (MMP-1) and MMP-3. Levels of sLOX-1 in the plasma and synovial fluid of patients with RA, compared with patients with osteoarthritis (OA), were determined by a specific chemiluminescence enzyme-linked immunoassay. In animal experiments, ox-LDL was injected into the knee joints of mice, with or without an anti-LOX-1 neutralizing antibody or sLOX-1, and the severity of arthritis was analyzed by histology and immunohistochemistry. **RESULTS:** Oxidized LDL and LOX-1 proteins were detected in the RA synovial tissue. Levels of MMP-1 and MMP-3 were enhanced by stimulation of RA FLS with ox-LDL, and the production of both MMPs was inhibited by blockade of the ox-LDL-LOX-1 interaction with the anti-LOX-1 neutralizing antibody or sLOX-1. Levels of sLOX-1 in the plasma and synovial fluid of RA patients were significantly higher than those in OA patients and healthy controls and were positively correlated with inflammation markers and the extent of RA disease activity. In the knees of mice, blockade of the ox-LDL-LOX-1 interaction suppressed arthritic changes and reduced the expression of MMP-3 induced by ox-LDL. **CONCLUSION:** These findings strongly indicate that sLOX-1 is a novel biomarker that may be useful for the diagnosis of RA and for the evaluation of disease activity in RA. Furthermore, the results suggest that LOX-1 may be a potent therapeutic target for RA.

NO	Title	Journal, Volume	Author(s)	Publication date	Abstract
32	Significance of Soluble Lectin-Like Oxidized LDL Recptor-1 Level in Systemic and Coronary Circulation in Acute Coronary Syndrome	BioMed Research International Volume 2014, Article ID 649185, 7 pages	Tomofumi Misaka, Yasuchika Takeishi	2014/2/1	**BACKGROUND:** Soluble lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) level is a novel biomarker for diagnosis of acute coronary syndrome (ACS); however, this level in the coronary circulation has yet to be examined. **METHODS:** Twenty-seven consecutive patients with ACS and 40 patients with effort angina pectoris (EAP) undergoing percutaneous coronary intervention (PCI) had levels of soluble LOX-1 and LOX-1 index measured in paired blood samples from aorta (Ao) and coronary sinus (CS) just prior to the PCI. **RESULTS:** We found positive correlations between soluble LOX-1 levels in the Ao and CS in both ACS and EAP patients ($P < 0.01$, for both). The soluble LOX-1 levels in the Ao and CS were higher in ACS than in EAP patients ($P < 0.01$, for both). The levels of soluble LOX-1 and LOX-1 index of the CS were significantly greater than those of the Ao in both ACS and EAP patients ($P < 0.01$, for both). Receiver operating characteristic curves for ACS detection demonstrated high sensitivity and specificity for the soluble LOX-1 and LOX-1 index with no differences between the Ao and CS. **CONCLUSIONS:** The present study showed that circulating soluble LOX-1 originates from coronary circulation and soluble LOX-1 and LOX-1 index are useful biomarkers for ACS.
33	Efficacy of High-Dose and Low-Dose Simvastatin on Vascular Oxidative Stress and Neurological Outcomes in Patient with Acute Ischemic Stroke: A Randomized, Double-Blind, Parallel, Controlled Trial	Hindawi Neurology Research International Volume 2018, Article ID 7268924, 6 pages	Nattapho Uranslip, Sombat Muengtaweepongsa	2018/7/8	**Backgrounds:** Stroke is the leading cause of death and long-term disability. Oxidative stress is elevated during occurrence of acute ischemic stroke (AIS). Soluble LOX-1 (sLOX-1) and NO are used as biomarkers for vascular oxidative stress that can reflect stabilization of atherosclerotic plaque. Previous study showed that simvastatin can reduce oxidative stress and LOX-1 expression. Objectives. To evaluate neurological outcomes and serum sLOX-1 and NO levels in patients with AIS treatment with low dose 10 mg/day and high dose 40 mg/day of simvastatin. **Methods:** 65 patients with AIS within 24 hours after onset were randomized to treatment with simvastatin 10 mg/day or 40 mg/day for 90 days. Personal data and past history of all patients were recorded at baseline. The blood chemistries were measured by standard laboratory techniques. Serum sLOX-1 and NO levels and neurological outcomes including NIHSS, mRS, and Barthel index were tested at baseline and Day 90 after simvastatin therapy. **Results:** Baseline characteristics were not significantly different in both groups except history of hypertension. Serum sLOX-1 and NO levels significantly reduce in both groups (sLOX-1 = and ng/ml; NO = and μmol/l) in 10 mg/day and 40 mg/day simvastatin groups, respectively. Neurological outcomes including NIHSS, mRS, and Barthel index significantly improve in both groups. However, no difference in NO level and neurological outcomes was found at 90 days after treatment as compared between low dose 10 mg/day and high dose 40 mg/day of simvastatin. **Conclusion:** High-dose simvastatin might be helpful to reduce serum sLOX-1. But no difference in clinical outcomes was found between high- and low-dose simvastatin. Further more intensive clinical trial is needed to confirm the appropriate dosage of simvastatin in patients with acute ischemic stroke. This trial is registered with ClinicalTrials.gov ID: NCT03402204.
34	Increased Levels of Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1 in Ischemic Stroke and Transient Ischemic Attack	J Am Heart Assoc. 2018 Jan 12;7(2). pii: e006479	Tonje Skarpengland, Tuva B. Dajl	2018/1/12	**BACKGROUND:** Soluble lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1) has been shown to be increased in patients with acute ischemic stroke. Here, we evaluated plasma sLOX-1 levels and vascular carotid plaque LOX-1 (ie, OLR1) gene expression in patients with ischemic stroke and transient ischemic attack (TIA) with particular focus on their relation to time since symptom onset. **METHODS AND RESULTS:** Plasma sLOX-1 (n=232) and carotid plaque OLR1 gene expression (n=146) were evaluated in patients who were referred to evaluation for carotid endarterectomy, as well as in healthy control plasma (n=81). Patients were categorized according to presence of acute ischemic stroke or transient ischemic attack (n=35) ≤7 days, >7 days ≤3 months (n=90), >3 months (n=40), or no reported symptoms before study inclusion (n=67). Our major findings were the following: (1) Patients with carotid atherosclerosis had increased plasma sLOX-1 levels as compared with controls. (2) Plaque OLR1 mRNA levels were increased in carotid plaques (n=146) compared with nonatherosclerotic vessels (ie, common iliac arteries of organ donors, n=10). (3) There were no differences in sLOX plasma levels or OLR1 gene expression when analyzed according to the time since relevant cerebral ischemic symptoms. (4) Also patients with severe carotid atherosclerosis without any previous ischemic events had raised sLOX-1 levels. (5) Immunostaining showed colocalization between LOX-1 and macrophages within the carotid plaques. (6) Also patients with acute stroke (within 7 days) caused by atrial fibrillation (n=22) had comparable raised sLOX-1 levels. **CONCLUSIONS:** sLOX-1 levels are elevated in patients with ischemic stroke and transient ischemic attack independent of cause and time since the ischemic event.

NO	Title	Journal, Volume	Author(s)	Publication date	Abstract
35	Oxidized low-density lipoprotein (oxLDL) affects load-free cell shortening of cardiomyocytes in a proprotein convertase subtilisin/kexin 9 (PCSK9)-dependent way	Basic Res Cardiol (2017) 112:63	Klaus-Dieter Schluter, Rainer Schulz	2017/9/14	Recent studies have documented that oxidized low-density lipoprotein cholesterol (oxLDL) levels directly impact myocardial structure and function. However, the molecular mechanisms by which oxLDL affects cardiac myocytes are not well established. We addressed the question whether oxLDL modifies load-free cell shortening, a standardized readout of cardiac cellular function, and investigated whether proprotein convertase subtilisin/kexin-9 (PCSK9) is involved on oxLDL-dependent processes. Adult rat ventricular cardiomyocytes were isolated and incubated for 24 h with oxLDL. PCSK9 was silenced by administration of siRNA. Load-free cell shortening was analyzed via a line camera at a beating frequency of 2 Hz. RT-PCR and immunoblots were used to identify molecular pathways. We observed a concentration-dependent reduction of load-free cell shortening that was independent of cell damage (apoptosis, necrosis). The effect of oxLDL was attenuated by silencing of oxLDL receptors (LOX-1), blockade of p38 MAP kinase activation, and silencing of PCSK9. oxLDL increased the expression of PCSK9 and caused oxidative modification of tropomyosin. In conclusion, we found that oxLDL significantly impaired contractile function via induction of PCSK9. This is the first report about the expression of PCSK9 in adult terminal differentiated ventricular cardiomyocytes. The data are important in the light of recent development of PCSK9 inhibitory strategies.
36	Oxidized LDL receptor LOX-1 is involved in neointimal hyperplasia after balloon arterial injury in a rat model	Cardiovascular Research 69 (2006) 263 – 271	Junichi Hinagata, et al.	2005/8/16	**Objective**: LOX-1 is a multi-ligand receptor originally identified as the endothelial oxidized LDL receptor. LOX-1 expression is also induced in smooth muscle cells in response to proinflammatory and oxidative stimuli. Here, we report on the role of LOX-1 in intimal hyperplasia, in which proinflammatory and oxidative stimuli are increased. **Methods and results**: Left common carotid artery of rat was injured by a balloon catheter. The expression of LOX-1 was significantly increased within 24 h after the balloon injury and peaked at day 7. LOX-1 expression was observed predominantly in medial smooth muscle cells until day 3, and then shifted to predominantly intimal smooth muscle cells. At day 14, the expression was concentrated in the regenerated endothelial cells. To examine the contributory role of LOX-1 in the growth of intimal smooth muscle cells, rats were administered anti-LOX1 antibody intravenously every 3 days after balloon injury. Anti-LOX-1 antibody administration effectively suppressed intimal hyperplasia, oxidative stress, and leukocyte infiltration compared with control IgG. These findings suggest the importance of LOX-1 expression in the pathogenesis of neointimal formation in conjunction with oxidative stress and leukocyte infiltration. **Conclusion**: The LOX-1 expressed in smooth muscle cells is involved in intimal hyperplasia in a rat model of balloon injury. Manipulation of LOX-1 activity is a novel potential therapeutic target to prevent restenosis after angioplasty.
37	Cross-talk between LOX-1 and PCSK9 in vascular tissues	Cardiovascular Research (2015) 107, 556–567 doi:10.1093/cvr/cvv178	Shijie Liu and Jawahar L. Mehta	2015/6/19	**Aims**: Lectin-like ox-LDL receptor-1 (LOX-1) plays an important role in inflammatory diseases, such as atherosclerosis. Proprotein convertase subtilisin/kexin type 9 (PCSK9) modulates LDL receptor degradation and influences serum LDL levels. The present study was designed to investigate the possible interaction between PCSK9 and LOX-1. **Method and results**: In the first set of experiments, human vascular endothelial cells and smooth muscle cells were studied at baseline and after lipopolysaccharide (LPS) treatment (to create an inflammatory state). Both PCSK9 and LOX-1 were strongly induced by LPS treatment. To define the role of PCSK9 in LOX-1 expression, cells were transfected with siRNA against PCSK9, which resulted in reduced LOX-1 expression and function. On the other hand, cells exposed to recombinant hPCSK9 revealed enhanced LOX-1 expression (P , 0.05). To determine whether LOX-1 also regulates PCSK9, cultured cells in which LOX-1 was knocked down by siRNA expressed less PCSK9, whereas those transfected with hLOX-1 cDNA showed increased PCSK9 expression. The second set of experiments was carried out in wild-type (WT) and gene knockout (KO; LOX-1 and PCSK9) mice; LOX-1 KO mice showed much less PCSK9 (P , 0.05 vs. WT mice). PCSK9-KO mice showed much less LOX-1 (P , 0.05 vs. WT mice). Furthermore, we observed that mitochondrial reactive oxygen species (mtROS) plays an initiating role in the LOX-1/PCSK9 interaction, since mtROS induction enhanced and its inhibition reduced the expression of both PCSK9 and LOX-1.We also found that both LOX-1 and PCSK9 regulate adhesion molecules vascular cell adhesion molecule-1 expression. Finally, oxidized low-density lipoprotein and tumour necrosis factor-a, pro-inflammatory stimuli besides LPS, regulated PCSK9 expression that is mediated by the NF-kB signalling pathway. **Conclusion**: These observations suggest that LOX-1 and PCSK9 positively influence each other's expression, especially during an inflammatory reaction. mtROS appear to be important initiators of PCSK9/LOX-1 expression.

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38	Relation of Serum ADMA, Apelin-13 and LOX-1 Levels with Inflammatory and Echocardiographic Parameters in Hemodialysis Patients	Therapeutic Apheresis and Dialysis 2018; 22(2):109-117 doi: 10.1111/1744-9987.12613	Yusuf Karavelioglu, et al	2017/12/4	**Abstract**: Cardiovascular diseases are the leading causes of mortality in patients with chronic kidney disease. Nitric oxide has a critical role in both endothelial dysfunction and the atherosclerosis process. We aimed to investigate the relationships between serum asymmetric dimethyl arginine (ADMA), LOX-1, and Apelin-13 levels, which are known to act over nitric oxide with endothelial dysfunction and cardiac morphology as well as with each other in hemodialysis patients. The study comprised a total of 120 patients (53 females and 67 males) receiving hemodialysis three times a week for at least 6 months and an age-gender matched control group (55 females and 58 males). Serum ADMA, LOX-1, and Apelin-13 levels were measured using the ELISA technique. Echocardiography, 24-h blood pressure monitoring by the Holter and carotid artery intima-media thickness (CIMT) measurement was performed on all of the included subjects. The associations between serum ADMA, LOX-1, and Apelin-13 levels with CIMT, echocardiographic parameters [left ventricular mass (LVM) and left ventricular mass index (LVMI)], and inflammatory markers [high sensitive Creactive protein (hsCRP) and neutrophil lymphocyte ratio (NLR)] were evaluated by correlation analysis. Serum ADMA, Apelin-13, and LOX-1 levels were significantly higher in the hemodialysis group than the controls ($P < 0.001$, $P < 0.001$, and $P < 0.001$, respectively). CIMT, hsCRP, and NLR levels were also significantly higher in the hemodialysis group ($P < 0.05$, $P < 0.001$, $P < 0.001$, respectively). Significant correlations were observed among the serum ADMA, Apelin-13, and LOX-1 levels. Moreover, notably positive correlations were found between these three biochemical markers and LVM, LVMI, hsCRP, and CIMT. Serum ADMA, Apelin-13, and LOX-1 levels can be indicators not only for the inflammatory process but also for the pathogenesis of cardiovascular diseases in hemodialysis patients. Key Words: Apelin-13, Asymmetric dimethyl arginine, Endothelial dysfunction, Hemodialysis, LOX-1.
39	Benifuuki Extract Reduces Serum Levels of Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1 Ligands Containing Apolipoprotein B A Double-Blind Placebo-Controlled Randomized Trial	Nutrients. 2018 Jul; 10(7): 924 doi: 10.3390/nu10070924	Masahiko Miyawaki, et al	2018/7/19	**Background:** Arteriosclerosis is associated with high levels of low-density lipoprotein (LDL) cholesterol. O-methylated catechins in "Benifuuki" green tea are expected to reduce cholesterol levels, although there is limited research regarding this topic **Methods:** This trial evaluated 159 healthy volunteers who were randomized to receive ice cream containing a high-dose of "Benifuuki" extract including 676 mg of catechins (group H), a low-dose of "Benifuuki" extract including 322 mg of catechins (group L), or no "Benifuuki" extract (group C). Each group consumed ice cream (with or without extract) daily for 12 weeks, and their lipid-related parameters were compared **Results:** A significant reduction in the level of lectin-like oxidized LDL receptor-1 ligand containing ApoB (LAB) was detected in group H, compared to groups L and C. No significant differences between the three groups were detected in their levels of total cholesterol, triglycerides, and LDL cholesterol **Conclusions:** "Benifuuki" extract containing O-methylated catechins may help prevent arteriosclerosis.
40	CKIP-1 limits foam cell formation and inhibits atherosclerosis by promoting degradation of Oct-1 by REG γ	NATURE COMMUNICATIONS | (2019) 10:425 doi.10.1038/s41467-018-07895-3	Jiao Fan. Lifeng Liu, Et al	2019/1/25	Atherosclerosis-related cardiovascular diseases are the leading cause of mortality worldwide. Macrophages uptake modified lipoproteins and transform into foam cells, triggering an inflammatory response and thereby promoting plaque formation. Here we show that casein kinase 2-interacting protein-1 (CKIP-1) is a suppressor of foam cell formation and atherosclerosis. Ckip-1 deficiency in mice leads to increased lipoprotein uptake and foam cell formation, indicating a protective role of CKIP-1 in this process. Ablation of Ckip-1 specifically upregulates the transcription of scavenger receptor LOX-1, but not that of CD36 and SR-A. Mechanistically, CKIP-1 interacts with the proteasome activator REG γ and targets the transcriptional factor Oct-1 for degradation, thereby suppressing the transcription of LOX-1 by Oct-1. Moreover, Ckip-1-deficient mice undergo accelerated atherosclerosis, and bone marrow transplantation reveals that Ckip-1 deficiency in hematopoietic cells is sufficient to increase atherosclerotic plaque formation. Therefore, CKIP-1 plays an essential antiatherosclerotic role through regulation of foam cell formation and cholesterol metabolism.
41	Higher serum lectin-like oxidized low-density lipoprotein receptor-1 in patients with stable coronary artery disease is associated with major adverse cardiovascular events: A multicentre pilot study	Biochem Med (Zagreb). 2019 Feb 15;29(1):010705. doi: 10.11613/BM.2019.010705	Zi-Wen Zhao, et al	2019/1/15	**INTRODUCTION:** Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is involved in the pathophysiology of atherosclerosis and acute coronary syndromes (ACS). Circulating soluble LOX-1 (sLOX-1) has been linked to the risk of coronary artery disease (CAD). Our aim was to test if baseline serum sLOX-1 was associated with major adverse cardiovascular events (MACE) in patients with stable CAD. **MATERIALS AND METHODS:** This multicentre pilot study enrolled 833 stable CAD patients. All patients were followed for two years. Serum sLOX-1 concentrations were detected by enzyme-linked immunosorbent assay (ELISA). The association between sLOX-1 concentrations and MACE was assessed by logistic regression, Kaplan-Meier survival curves and Cox proportional hazards analyses. Logistic regression analysis was employed to assess the predictors of complex lesion. **RESULTS:** Multivariate logistic regression analysis revealed that sLOX-1 concentration was an independent predictor of MACE (OR 2.07, 95%CI 1.52 - 2.82; $P < 0.001$). Kaplan-Meier cumulative survival curves showed that the incidence of MACE in patients with a high sLOX-1 concentration was significantly higher than in patients with an intermediate or low sLOX-1 concentration ($P < 0.001$). Soluble LOX-1 concentrations were independently correlated with coronary complex lesions (OR 2.32, 95%CI 1.81 - 2.97; $P < 0.001$). **CONCLUSIONS:** Baseline sLOX-1 concentrations were correlated with 2-year MACE in stable CAD patients. Furthermore, patients with high serum sLOX-1 concentrations had higher cumulative incidence of MACE compared to those with low serum sLOX-1 concentrations.

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42	High Levels of Soluble Lectinlike Oxidized Low-Density Lipoprotein Receptor-1 Are Associated With Carotid Plaque Inflammation and Increased Risk of Ischemic Stroke	J Am Heart Assoc. 2019;8:e009874. DOI: 10.1161/JAHA.118.009874	Hanna Markstad. Andreas Edsfeldt, et al	2019/2/12	**Background**—When the lectinlike oxidized low-density lipoprotein (oxLDL) receptor-1 (LOX-1), a scavenger receptor for oxLDL,binds oxLDL, processes leading to endothelial dysfunction and inflammation are promoted. We aimed to study release mechanismsof LOX-1 and how circulating levels of soluble LOX-1 (sLOX-1) relate to plaque inflammation and future risk for ischemic stroke. **Methods and Results**—Endothelial cells and leukocytes were used to study release of sLOX-1. Plasma levels of sLOX-1 were determined in 4703 participants in the Malm€o Diet and Cancer cohort. Incidence of ischemic stroke was monitored. For 202 patients undergoing carotid endarterectomy, levels of sLOX-1 were analyzed in plasma and plaque homogenates and related to plaque inflammation factors. Endothelial cells released sLOX-1 when exposed to oxLDL. A total of 257 subjects experienced stroke during a mean follow-up of 16.5 years. Subjects in the highest tertile of sLOX-1 had a stroke hazard ratio of 1.75 (95% CI, 1.28-2.39) compared with those in the lowest tertile after adjusting for age and sex. The patients undergoing carotid endarterectomy had a significant association between plasma sLOX-1 and the plaque content of sLOX-1 (r=0.209, P=0.004). Plaques with high levels of sLOX-1 had more oxLDL, proinflammatory cytokines, and matrix metalloproteinases. **Conclusions**—Our findings demonstrate that oxLDL induces the release of sLOX-1 from endothelial cells and that circulating levels of sLOX-1 correlate with carotid plaque inflammation and risk for ischemic stroke. These observations provide clinical support to experimental studies implicating LOX-1 in atherosclerosis and its possible role as target for cardiovascular intervention.