ORIGINAL RESEARCH

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Serum sLOX-1 levels are associated with the presence and severity of angiographic coronary artery disease in patients with metabolic syndrome

Abstract

Purpose: Patients with metabolic syndrome are at high-risk for development of atherosclerosis and cardiovascular events. Serum soluble lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1) is associated with coronary artery disease (CAD) and metabolic disorders. We sought to assess whether serum sLOX-1 levels are correlated with the presence and severity of CAD in patients with metabolic syndrome (MetS) undergoing coronary angiography.

Methods: Serum sLOX-1 levels were measured in 112 consecutive patients with MetS, undergoing coronary angiography for the evaluation of CAD. The severity of CAD was assessed by angiographic Gensini score system.

Results: Serum sLOX-1 levels were significantly higher in MetS patients with CAD (n=69) than in those without CAD (n=43) (0.925 [range 0.137 to 1.432] ng/ml *vs.* 0.207 [range 0.063 to 0.774] ng/ml, $P<0.01$). Multivariate logistic regression analysis revealed that serum sLOX-1 level was independently associated with the presence of CAD (odds ratio 2.489, 95% confidence interval 1.290-4.802; $P<0.01$). Serum sLOX-1 levels were positively correlated with the Gensini score (ρ : 0.394, $P<0.01$) after adjusting for other clinical characteristics.

Conclusions: High sLOX-1 levels are associated with the presence and severity of CAD in patients with MetS. The measurement of serum sLOX-1 may be potentially useful in predicting the presence and severity of CAD in patients with MetS.

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Many epidemiological and clinical studies have confirmed the association between metabolic syndrome (MetS) and increased risk for coronary artery disease (CAD), which is the leading cause of mortality worldwide [1,2]. Morbidity and mortality from CAD are higher in patients with MetS [1]; therefore, early assessment of the risk of CAD in patients with MetS is desirable because it could lead to improved patient or physician adherence to risk-reducing behaviors or interventions and improve clinical outcomes.

Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), a type II membrane glycoprotein, was initially identified as the major receptor for oxidized low-density lipoprotein (ox-LDL) in endothelial cells (ECs) and was later found also to have an inducible expression in macrophages and vascular smooth muscle cells (VSMCs) [3,4]. Like many cell-surface receptors with a single transmembrane domain, LOX-1 can be proteolytically cleaved at its membrane proximal extracellular domain and released as a soluble form (sLOX-1) [5]. The level of circulating sLOX-1 may reflect the expression of LOX-1 [6], and is increasingly viewed as a biomarker for CAD. Circulating sLOX-1 levels are elevated in patients with acute coronary syndrome (ACS) [7] and are associated with inflammatory markers and oxidative stress markers in patients with CAD [8,9]. More recently, a prospective study has demonstrated that higher LOX index values are associated with an increased risk of coronary vascular disease in the general population [10]. Meanwhile, there is increasing evidence that increased LOX-1 expression is related to adipocyte metabolism and plays an important role in the development of metabolic disorders. Circulating sLOX-1 levels are significantly increased in obesity [11], in type 2 diabetes mellitus [12], and is correlated with body weight, BMI and total body fat [11]. In addition, Nomata *et al.* recently reported that weight reduction can decrease circulating sLOX-1 levels in overweight middle-aged men [13]. The pathophysiologic role of LOX-1 in atherogenesis associated with MetS is still unknown: the precise relationship between the sLOX-1 levels and the presence and severity of CAD in patients with MetS remains unclear. We, therefore, aimed at clarifying the link between circulating sLOX-1 levels and the angiographic presence and severity of CAD in patients with MetS.

Methods

Study population

From May 2008 to December 2009, a total of 255 consecutive patients with MetS underwent coronary angiography for the evaluation of CAD in our hospital. MetS was defined using the

updated National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) criteria for Asian Americans as having ≥ 3 of the following components: waist circumference ≥ 90 cm for men or ≥ 85 cm for women; triglycerides ≥ 1.7 mmol/L; HDL cholesterol < 1.03 mmol/L for men or < 1.7 mmol/L for women; blood pressure $\geq 130/85$ mmHg or current use of antihypertensive medications; or fasting glucose ≥ 5.6 mmol/L [14]. Diabetic patients were excluded from this study to avoid the contribution of diabetes as a potential confounder. Patients with acute coronary syndromes, previously documented CAD, suspected myocarditis or pericarditis, malignant disease, active inflammatory disease or advanced renal disease were also excluded. In total, 112 consecutive patients with MetS were enrolled in this study.

All patients gave written informed consent for their participation. This study was approved by the Ethics Committee of Fourth Military Medical University and conformed to the principles outlined in the Declaration of Helsinki.

Coronary angiography analysis

Conventional invasive coronary angiography was performed according to standard protocols by interventional cardiologists blinded to the study protocol. Angiographic CAD in patients was defined as coronary artery stenosis of $\geq 50\%$. Severity of coronary stenosis in patients was estimated by the Gensini coronary score [15]. The Gensini system scores the narrowing of the coronary artery lumen as follows: a score of 1, 1-25% narrowing; 2, 26-50% narrowing; 4, 51-75% narrowing; 8, 76-90% narrowing; 16, 91-99% narrowing; and 32, total occlusion. The score was then multiplied by a factor that incorporated the importance of the lesion's position in the coronary arterial tree: for example, 5 for the left main coronary artery, 2.5 for the proximal left anterior descending (LAD) or proximal left circumflex coronary artery (LCX), 1.5 for the mid-LAD, and 1 for the distal LAD or mid-distal LCX.

Blood chemistry analysis

Venous blood samples of all 112 patients were obtained in a 12 hour fasting state just before the angiographic procedure. The samples were immediately centrifuged at 3000 g for 10 min and frozen at -70°C until analysis. Serum total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) were measured by standard laboratory techniques on a Hitachi 7600 Automatic Biochemical Analyzer (Hitachi Co., Japan). Serum sLOX-1 level was determined using a commercially available enzyme-linked immunosorbent assay (ELISA) kit

(USCN, Wuhan, China). The lower limit of the detection for sLOX-1 was 2.4pg/ml. This ELISA kit has high sensitivity and excellent specificity for detection of human sLOX-1. No significant cross-reactivity or interference with CD94, LDL, HDL or VLDL was observed. Preliminary data obtained in our laboratory showed that the coefficient of variation was <5%.

Statistical analysis

Sample size was determined by power analysis using preliminary data obtained in our laboratory with the following assumptions: α of 0.05 (two-tailed), power of 80%, an expected CAD rate of 60% in patients with Mets, difference in sLOX-1 levels between patients with and without Mets of 0.50 ng/ml, and a standard deviation of 0.50 ng/ml. Therefore, a minimum of 35 patients would detect a difference in the sLOX-1 levels (16). Statistical analysis was performed using SPSS 10.0 (SPSS Inc, IL, USA). Results of normally distributed continuous variables were expressed as the mean value $\pm$ SD, and those for continuous variables with skewed distribution were expressed as the median value (interquartile range). Comparisons between groups were performed using the unpaired *t*-test, Mann-Whitney *U* test, or Chi-square test as indicated. Univariate analysis was performed and the variables with a $P < 0.10$, as well as pharmacological treatment factors, were then entered into a backward stepwise multivariate logistic regression model to assess the independent predictors for the presence of CAD. Pearman rank correlation coefficient was performed and the variables with a $P < 0.10$ were then entered into a multiple regression analysis to assess the independent predictors of Gensini score. As the Gensini score and serum sLOX-1 levels were not normally distributed, logarithmic (log) transformed values were used for multivariate regression analysis. As there were patients with Gensini: 0, log (Gensini+0.5) transformation was used as the dependent variable. Statistical significance was defined as $P < 0.05$.

Results

Baseline clinical characteristics

Patients were grouped according to the presence or absence of angiographic CAD, and their baseline characteristics are shown in Table 1. There were no significant differences in age, waist circumference, body mass index (BMI), systolic or diastolic blood pressure between the two groups (all $P > 0.05$). Also, the two groups were similar in terms of serum levels of fasting glucose ($P = 0.970$), TC ($P = 0.845$), TG ($P = 0.944$) and HDL-C ($P = 0.686$). There were significant differ-

TABLE 1. Baseline clinical characteristics

Variables	Without CAD (n=43)	With CAD (n=69)	P value
Age (years)	56.5 $\pm$ 11.6	61.3 $\pm$ 9.1	0.053
Male, n (%)	20 (46.5%)	47 (68.1%)	0.014 ^a
Waist circumference (cm)	85.4 $\pm$ 7.1	86.9 $\pm$ 7.5	0.464
BMI (Kg/mm ²)	25.1 $\pm$ 2.7	26.0 $\pm$ 2.7	0.894
SBP (mm/Hg)	133.9 $\pm$ 12.5	133.8 $\pm$ 14.6	0.487
DBP (mmHg)	81.9 $\pm$ 11.1	81.6 $\pm$ 10.9	0.934
FBG (mmol/L)	5.58 $\pm$ 0.60	5.56 $\pm$ 0.62	0.970
TC (mmol/L)	4.42 $\pm$ 0.97	4.67 $\pm$ 1.03	0.845
TG (mmol/L)	1.83 $\pm$ 0.85	2.02 $\pm$ 0.86	0.944
LDL-C (mmol/L)	2.69 $\pm$ 0.75	2.81 $\pm$ 1.05	0.013 ^a
HDL-C (mmol/L)	1.08 $\pm$ 0.21	1.00 $\pm$ 0.19	0.686
Treatment before/on admission			
Statins, n (%)	13, (30.2%)	19, (27.5%)	0.396
ACEI/ARB n (%)	18, (41.9%)	26, (37.7%)	0.572

All values are mean $\pm$ SD or n (%). BMI= body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure, FBG=fasting glucose, TC=total cholesterol, TG=triglycerides, LDL-C= low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, ACEI= angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker. ^a Statistically significant.

ences with respect to gender ($P = 0.014$) and LDL-C ($P = 0.013$) between patients with CAD and those without CAD.

Relationship between sLOX-1 levels and CAD

As shown in Fig.1, MetS patients with CAD had significantly higher serum sLOX-1 levels than those without CAD (0.925 (range 0.137 to 1.432) ng/ml vs. 0.207 [range 0.063 to 0.774] $P < 0.01$). Simple logistic regression analysis showed that age (OR 1.048, 95% CI 1.008 to 1.091; $P = 0.020$), gender (OR 2.457, 95% CI 1.121 to 5.384; $P = 0.025$), BMI (OR 1.132, 95% CI 0.979 to 1.309; $P = 0.093$), HDL-C (OR 0.116, 95% CI 0.016 to 0.851; $P = 0.034$) and sLOX-1 levels (OR 2.191, 95% CI 1.198 to 4.008; $P = 0.011$) showed a trend ($P < 0.10$) toward an association with the presence of angiographic CAD (Table2). All these variables and pharmacological treatment factors were then entered into a backward stepwise multivariate logistic regression model. Multivariate logistic regression of revealed that sLOX-1 levels remained as a significant and independent predictor of angiographic CAD (odds ratio 2.489, 95% confidence interval 1.290-4.802; $P < 0.01$) (Table2).

Association of sLOX-1 levels with the Gensini score

In MetS patients with CAD, a significant positive correlation was found between serum sLOX-1 levels and Gensini score (ρ : 0.394, $P = 0.001$) (Fig.2, Table3). In addition, Gensini score was significantly

FIGURE 1. Box-and-whisker plot showing serum sLOX-1 levels between the patients with CAD and without CAD.
CAD=coronary artery disease

FIGURE 2. Correlations between serum sLOX-1 and the severity of CAD evaluated by Gensini score.
CAD=coronary artery disease.

TABLE 2. Logistic regression Analysis for the presence of angiographic CAD

Variables	Simple regression		Multiple regression	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (per year)	1.048 (1.008-1.091)	0.020	1.081 (1.030-1.136)	0.002
Male (yes)	2.457 (1.121-5.384)	0.025	1.878 (0.738-4.780)	0.186
Waist circumference (per cm)	1.028 (0.976-1.084)	0.297		
BMI (per Kg/mm ²)	1.132 (0.979-1.309)	0.093	1.250 (1.030-1.517)	0.024
SBP (per mm/Hg)	0.999 (0.972-1.027)	0.952		
DBP (per mmHg)	0.998 (0.963-1.034)	0.902		
FBG (per mmol/L)	0.931 (0.497-1.745)	0.823		
TC (per mmol/L)	1.285 (0.875-1.887)	0.200		
TG (per mmol/L)	1.295 (0.815-2.057)	0.274		
LDL-C (per mmol/L)	1.143 (0.759-1.722)	0.521		
HDL-C (per mmol/L)	0.116 (0.016-0.851)	0.034	0.154 (0.016-1.468)	0.104
Statins (yes)	0.877 (0.379-2.028)	0.759	0.505 (0.181-1.410)	0.192
ACEI/ARB (yes)	0.840 (0.386-1.827)	0.660	0.726 (0.291-1.806)	0.491
sLOX-1(per ng/ml)	2.191 (1.198-4.008)	0.011	2.489 (1.290-4.802)	0.007

OR=odds ratio, CI=confidence interval, other abbreviations are as in Table 1.

correlated with age ($p: 0.238$, $P=0.049$) and HDL-C ($p: -0.261$, $P=0.030$) (Table 3). Multivariate regression model including age, BMI, HDL-C, log (sLOX-1) and sex (as a confounding factor) showed that age ($\beta: 0.177$, 95%CI: 0.001-0.024) and log (sLOX-1) ($\beta: 0.312$, 95%CI: 0.136-0.465) were the only significant predictors of log (Gensini score).

Discussion

MetS patients with CAD have significantly higher serum sLOX-1 levels than those without CAD, and that the serum level of sLOX-1 is an independent predictor of the presence of angiographically significant CAD. Furthermore, among patients with CAD, serum sLOX-1 levels were significantly associated with the angiographic severity of CAD. This is the first study that addresses the relationship between sLOX-1 levels and CAD in patients with MetS.

Due to the current epidemic of obesity and the increasingly sedentary lifestyle in developed and newly industrialized countries, the prevalence of the MetS is very high in large parts of the world [17]. MetS is a common basis for the development of atherogenic cardiovascular diseases especially CAD [18]. Therefore, early prediction of the risk of the CAD in patients with MetS is of critical importance. In recent years, noninvasive blood biomarkers have emerged as important tools for diagnosis, risk stratification and therapeutic decision-making for patients with cardiovascular disease [19]; however, few studies have investigated the blood biomarkers for the presence and severity of CAD in patients with MetS [20].

The major finding of the present study was that among patients with MetS referred to coronary angiography, high serum sLOX-1 levels were significantly associated with the presence of angiographically-significant CAD. This finding may help to explain the missing cross-talk between MetS and cardiovascular complications resulting from metabolic disorders. MetS is characterized by a clustering of cardiovascular risk factors including hyperglycemia, obesity, dyslipidemia and hypertension [21]. The involvement of LOX-1 in the development of atherosclerosis resulting from MetS has been suggested by the fact that the cardiovascular risk factors of MetS are closely associated with the upregulation of LOX-1. Dyslipidemia, particularly increased plasma level of ox-LDL, plays the major role in the upregulation of LOX-1 [22]. Moreover, Taye *et al.* demonstrated that hyperglycemia-induced generation of reactive oxygen species (ROS) contributed to LOX-1 upregulation in human endothelial cells [23]. Hu *et al.* reported that angiotensin II mediated hypertension upregulated the expression of LOX-1 [24]. Recent studies have also found that circulating levels of sLOX-1 are significantly increased in metabolic disorders,

TABLE 3. Correlation analysis between the clinical characteristics and the Gensini score

Variables	log (Gensini Score)	
	Correlation coefficient	P value
Age (years)	0.238	0.049 ^a
Waist circumference (cm)	0.007	0.953
BMI (Kg/mm ²)	0.046	0.070
SBP (mm/Hg)	-0.116	0.343
DBP (mmHg)	-0.042	0.730
FBG (mmol/L)	-0.149	0.222
TC (mmol/L)	-0.206	0.109
TG (mmol/L)	-0.088	0.470
LDL-C (mmol/L)	-0.037	0.764
HDL-C (mmol/L)	-0.261	0.030 ^a
log (sLOX-1[ng/ml])	0.394	0.001 ^a

Abbreviations are as in Table 1. ^aStatistically significant

including obesity [11] and type 2 DM [12], and are positively correlated with reduction in body weight [13]. The activation of LOX-1 is involved in endothelial ECs dysfunction [25], apoptosis of VSMCs [26], accumulation of lipids in macrophages [27], and production of matrix metalloproteinases [28], resulting in cell injury that facilitates atherosclerotic plaque formation and progression. Our results suggest that LOX-1 plays a pivotal role in the cross-talk between MetS and CAD, and high sLOX-1 level could perhaps be used to predict the occurrence of future cardiovascular events in patients with MetS.

We also assessed the relationship between sLOX-1 levels and the severity of CAD, as assessed by Gensini coronary severity score. There are various methods to evaluate the angiographic severity, including Gensini scoring system, cumulative coronary artery stenosis scoring system, Hamsten scoring system and AHA scoring system [15,29,30]. As Gensini score is more effective and gives numeric objective data in comparison with other systems [31] this method was used to determine the severity of CAD. Consistent with previous studies showing that sLOX-1 levels are up-regulated during CAD progression [8], our data demonstrated that sLOX-1 level was significantly correlated with angiographic Gensini score in CAD patients. These results suggest that sLOX-1 might play a key role in the progression of atherosclerotic plaque; however, the association between sLOX-1 levels and Gensini score was weak and its clinical significance has yet to be determined.

The potential limitations of these data merit consideration. First, this study was cross-sectional, thereby allowing the determination of associations, but not formulation of risk predictions. In addition, the study populations were relatively small.

Therefore, our findings need further investigation in prospective studies with larger sample size. Second, all the patients included were referred for coronary angiography because of the occurrence of cardiac symptoms or positive stress test. These might have resulted in increased prevalence of CAD in the study populations. Third, the MetS in our study was defined by NCEP/ATP III criteria for Asian Americans [14] because the “harmonized” MetS criteria for Chinese patients [32] had not yet announced when we began the study. The difference between the two criteria might contribute to selection bias of MetS patients. Last, sLOX-1 levels might be higher in MetS patients than in general population [10-12]. Therefore, a normal control group should be included in future studies to evaluate the degree of impact that the presence and severity of CAD can give on sLOX-1 levels and to better understand the role of MetS in the increment of sLOX-1 levels. In conclusion, our study demonstrates serum sLOX-1 levels are significantly higher in the presence of CAD and are correlated with the severity of the disease in patients with MetS. If these results are confirmed by further clinical studies, sLOX-1 level may prove to be a promising biomarker for the detection and risk assessment of CAD in patients with MetS.

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