Circulating Soluble Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1 Levels Are Associated With Erectile Dysfunction in Patients Without Known Coronary Artery Disease

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ABSTRACT

Aim. Endothelial dysfunction and microvascular damage are involved in the pathogenesis of erectile dysfunction (ED). Soluble lectin-like oxidized low-density lipoprotein receptor-1 (sLOX-1) is identified endothelial receptor for oxidized low-density lipoprotein (ox-LDL) that plays a pivotal role in ox-LDL-induced endothelial dysfunction. The purpose of the current study was to determine the association between sLOX-1 and ED in patients without known coronary artery disease (CAD).

Main Outcome Measures. Diagnosis of ED was based on the International Index of Erectile Function Score-5. Levels of sLOX-1 were measured in serum by enzyme-linked immunosorbent assay.

Methods. One hundred thirty-eight subjects with ED patients without known CAD (ED group) and 75 age-matched subjects without ED and known CAD (Non-ED Group) were included in this study.

Results. Plasma levels of sLOX-1 were significantly higher in ED than in Non-ED group (95 ± 87 and 49 ± 30 pg/mL, respectively, $P < 0.001$). The levels of sLOX-1 highly negative correlated with score of ED ($r = -0.618$, $P < 0.001$). The sLOX-1 levels >75 pg/mL predicts ED with 26.8% sensitivity and 96.0% specificity on receiver operator characteristic analysis.

Conclusions. Our study demonstrated that serum sLOX-1 levels were associated with endothelial dysfunction that predicts ED. Moreover, the current study revealed that there was strong negative correlation between the levels of circulating sLOX-1 and score of ED. This study suggested sLOX-1 may be involved in the pathogenesis of ED in patients without known CAD. **Kobat MA, Fırdolas F, Balin M, Çelik A, Bentli R, and Baydas A. Circulating soluble lectin-like oxidized low-density lipoprotein receptor-1 levels are associated with erectile dysfunction in patients without known coronary artery disease. J Sex Med 2013;10:2782–2789.**

Key Words. Endothelial Function; Erectile Dysfunction; Microvascular Damage; Soluble Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1

Introduction

Erectile dysfunction (ED) is defined as the inability to achieve or maintain penile erection with sufficient quality to perform satisfactory sexual intercourse [1]. It is the most common sexual problem in men and is now believed to be another manifestation of atherosclerotic vascular disease [2]. It is estimated that nearly one half of men older than 40 years are sufferers of ED to some degree [3]. Recent data demonstrate that ED is associated with impaired endothelial-dependent flow-mediated dilatation (FMD), suggesting that ED is associated with endothelial dysfunction [4]. In addition, some other studies have shown that the presence of subclinical coronary artery disease (CAD), as assessed by angiography and multislice tomography, is directly correlated with the severity of ED [5,6]. In addition, the common risk factors, hypertension, dyslipidemia, smoking, obesity, diabetes mellitus, and sedentary lifestyle, for endothelial dysfunction and atherosclerosis have been frequently found in patients with ED [7,8]. Atherosclerosis is a systemic disorder and involves

different vascular beds [9]. Actually, endothelial dysfunction precedes the development of atherosclerosis and predisposes to the development of structural vascular damage [10].

The oxidized low-density lipoprotein (ox-LDL) is recognized as a major cause of endothelial dysfunction in atherosclerosis [11]. ox-LDL has been suggested to affect endothelium-dependent vascular tone through a decreased biological activity of endothelium-derived nitric oxide (NO) and mediates several of its biological effects via lectin-like ox-LDL receptor-1 (LOX-1) [12]. The induced expression of LOX-1 in endothelial cells may provide a molecular link for incorporation of ox-LDL into the cells, resultant cellular activation, and dysfunction. In addition, ox-LDL bound to LOX-1 induces the generation of superoxide anions [13] that inactivate NO and activate nuclear factor-kB [14], CD40/CD40L [15], and subsequently induce upregulation in the expression of vasoconstrictive molecules (endothelin-1), adhesion molecules (*P*-selectin, vascular cell adhesion molecule, intercellular adhesion molecule-1), and chemokines (monocyte chemotactic protein-1) [16]. LOX-1 is cleaved from the cell surface by certain proteases and released as soluble LOX-1 form (sLOX-1) that can be measured in the serum [17]. Because the level of soluble receptors in circulating blood may reflect the expression of membrane proteins and disease activities, sLOX-1 may be a potential biomarker of vascular disease assessment. We sought to determine whether any relationship exists between ED and the level of sLOX-1. To our knowledge, this is the first study to assess the serum sLOX-1 level in patients with ED without known CAD.

Materials and Methods

Patient Population

The present study included 138 patients suffering from ED for >1 year among those presenting to the andrology outpatient clinic. In addition, 75 age-matched male volunteers without ED were enrolled as a control group. All participants provided written informed consent to participate in the study. The study protocol was approved by the local ethics committee, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice/International Conference on Harmonization guidelines.

All patients had: a complete detailed and careful history taken, with special attention to the sexual history, including details to differentiate between psychogenic and organic ED; a complete physical examination, including genital and neurological examination; blood glucose assay, urine analysis, complete blood assessment, and kidney and liver function; hormonal assays of testosterone, prolactin, and thyroxin; combined intracavernosal injection and stimulation with a standard dose of 1-mL papaverine HCl (30 mg).

Assessment of Erectile Function

Erectile function was assessed using the abridged five-item version of the International Index of Erectile Function questionnaire (IIEF-5), a validated, self administered questionnaire [18]. Possible scores for the IIEF-5 range from 5 to 25; scores of 22–25 indicate normal erectile function, while scores of 21 or below indicate ED [18]. According to the IIEF-5 score, ED can be classified as severe (5–7), moderate (8–11), mild-to-moderate (12–16), or mild (17–21).

Exclusion criteria included: congestive heart failure (ejection fraction <50%), previous myocardial infarction, suspected myocarditis or pericarditis, pulmonary hypertension, stroke, known peripheral atherosclerotic disease, surgical coronary intervention, other major vascular surgical procedures, percutaneous coronary angioplasty and/or stenting, stable and unstable angina pectoris, impaired renal function (creatinine ≥1.4 mg/dL), unstable endocrine or metabolic diseases (e.g., hypoprolactinemia and hyperprolactinemia, hypoandrogenic and hyperandrogenic states, hypothyroidism and hyperthyroidism), and patients with concomitant inflammatory diseases such as infections and autoimmune disorders, acute/chronic hepatic or hepatobiliary disease, and malignancy. Patients taking beta-blocker, spironolactone, corticosteroids, antioxidant vitamins, and alcohol were also excluded from the study. Also ineligible were men who failed to achieve an erection after radical prostatectomy or pelvic surgery, and those who had penile implants, clinically noteworthy penile deformities, and a history of spinal-cord trauma within 12 months of study onset.

Blood Sampling and Laboratory Methods

Blood samples of all individuals were taken from an antecubital vein following an overnight fasting state. After centrifugation at $3{,}000 \times g$ for 10 minutes, serum and plasma samples were frozen and stored at −80°C until an assay could be performed. Serum sLOX-1 levels were measured by a commercially available enzyme-linked immunosorbent assay kit. The detection limit for serum

Table 1 The baseline characteristic properties of study patients

	ED group (N = 138)	Control group (N = 75)	*P* value
Age (years)	58 ± 10	56 ± 10	0.09
History of (%)			
Diabetes mellitus	35	29	0.2
Hypertension	37	32	0.2
Smoke	61	57	0.3
Family history of CAD	20	21	0.4
Fasting glucose (mg/dL)	109 ± 33	106 ± 27	0.5
Creatinin (mg/dL)	0.7 ± 0.2	0.7 ± 0.1	0.1
Triglyceride (mg/dL)	187 ± 73	191 ± 70	0.6
Total cholesterol (mg/dL)	210 ± 26	208 ± 26	0.4
LDL-C (mg/dL)	128 ± 18	126 ± 20	0.4
HDL-C (mg/dL)	43 ± 10	45 ± 11	0.1
sLOX-1 (pg/mL)	95 ± 87	49 ± 30	<0.001
Systolic BP (mm Hg)	123 ± 13	120 ± 14	0.1
Diastolic BP (mm Hg)	76 ± 10	74 ± 11	0.1
Heart rate (beat/minute)	68 ± 11	66 ± 8	0.1
BMI (kg/m^2)	27.4 ± 3.2	25.2 ± 2.9	<0.001
Waist circumference (cm)	97 ± 7	93 ± 6	<0.001
ED score	14 ± 17	23 ± 1	<0.001

$P < 0.05$ was accepted as statistically significant.
BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; ED = erectile dysfunction; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; sLOX-1 = soluble lectin-like oxidized low-density lipoprotein receptor-1

sLOX-1 level was 2.4 pg/mL, with a coefficient of variation <5%. Analyses were performed by the immunologists, who were blinded to the condition of the samples. Triglyceride (TG), total cholesterol (Total-C), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) concentrations were measured by automated chemistry analyzer (Roche Diagnostics, Indianapolis, IN, USA) by using commercially available kits.

Statistical Analysis

Continuous variables were given as mean ± standard deviation, and categorical variables were defined as percentages. Comparisons between two groups were carried out using an independent samples *t*-test and chi-square test. Comparisons between the grade of ED were carried out using one-way analysis of variance and Tukey post-hoc test. Correlation analyses were performed using the Pearson's or Spearman's coefficient of correlation. Sensitivity and specificity values of sLOX-1 levels for predicting ED were estimated using receiver operator characteristic (ROC) curve analysis. The cutoff level of sLOX-1 levels were determined using by using MedCalc 9.2.0.1 (MedCalc Software, Mariakerke, Belgium). SPSS 15.0 software was used for basic statistical analysis (Version 15, SPSS, Inc., Chicago, IL, USA). A value of $P < 0.05$ was accepted as statistically significant.

Results

The baseline characteristic properties of study patients were summarized in Table 1. There were no significant differences between two groups with respect to age, frequencies of major coronary risk factors (i.e., diabetes mellitus, hypertension, smoking, family history of CAD), fasting glucose, hemoglobin A1c, serum creatinine, Total-C, LDL-C, HDL-C, TG, heart rate, and systolic and diastolic blood pressure ($P > 0.05$ for all). There were no significant differences at the usage of asetilsalysilic acid, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, statin, and calcium channel blockers between two groups. Otherwise, subjects who used statin regularly had significantly lower sLOX-1 levels than subjects who never used statin therapy (86 ± 81 pg/mL; N = 146 and 63 ± 56 pg/mL; N = 47, respectively, $P = 0.02$). The sLOX-1 levels were highly negative correlated with ED score (r = –0.618, $P < 0.001$).

The values of body mass index (BMI), waist circumferences and sLOX-1 levels were higher in patients in ED group than Non-ED group (Table 1). The sLOX-1 levels were significantly increased with the grade of ED as mild-to-severe (Figure 1). The sLOX-1 levels were not correlated with BMI (r = 0.065, $P = 0.347$).

In Figure 2, an ROC curve is used to identify the ability of sLOX-1 levels to predict the ED. The area under the ROC curve was 0.649 for the sLOX-1 levels ($P = 0.0001$). The sensitivity and

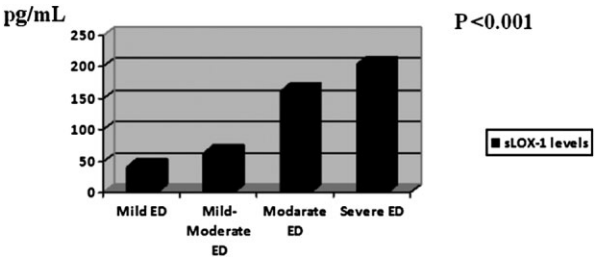

Figure 1 The distribution of sLOX-1 levels according to the degree of erectile dysfunction (ED) (40.5 ± 30.5 pg/mL [mild; n = 49], 62.6 ± 23.5 pg/mL [mild-moderate; n = 41], 160.0 ± 97.6 pg/mL [moderate; n = 28] and 204.3 ± 93.8 pg/mL [severe; n = 20], respectively, $P < 0.001$).

specificity values of the sLOX-1 levels were 26% and 8%, and 96% and 0%, respectively (cutoff value was 75 pg/mL).

Discussion

This study demonstrated the association between the levels of circulating sLOX-1 and ED in men without known CAD. The results of this study showed that among subjects without known CAD, those with ED had significantly higher circulating sLOX-1 levels than those without ED. Moreover, the current study revealed that there was a strong negative correlation between the levels of circulating sLOX-1 and score of ED. To the best of our knowledge, this is the first study to show that the serum levels of sLOX-1 represent a marker of ED patients. This study suggested that sLOX-1 might be a useful biomarker that plays crucial role in pathophysiology of ED in patients without known CAD.

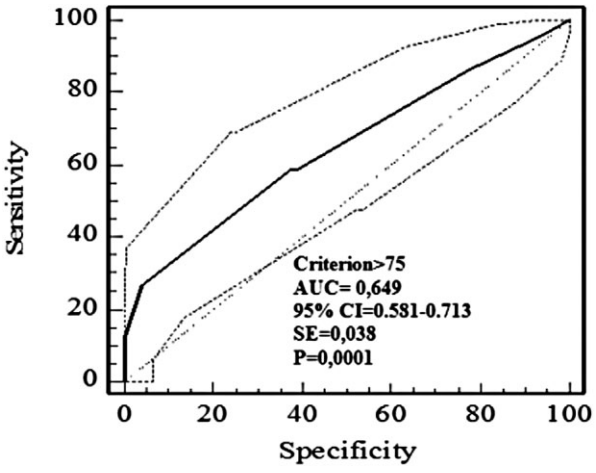

Figure 2 ROC curve of sLOX-1 levels in study patients for erectile dysfunction. AUC = Area under curve; SE = Standard error; CI = confidence interval (sensitivity 26.8% and specificity 96.0%).

ED is caused by two main, organic and psychogenic, etiologies. ED because of organic causes comprise up to 80% of cases; at the same time, vascular disease is the most common pathophysiology of ED [7]. The common risk factors for endothelial dysfunction and atherosclerosis have been frequently found in patients with ED [7,8]. It was generally accepted that ED has been associated with advanced atherosclerotic CAD [2,19]. But now, several other studies have also reported that endothelial dysfunction in the penile circulation accompanies ED in association with various cardiovascular risk factors without advanced atherosclerotic disease [20,21]. Elesber et al. [22] demonstrated for the first time the association between coronary endothelial dysfunction and an increased prevalence of ED in men without obstructive CAD. Furthermore, this study demonstrated that the severity of coronary endothelial dysfunction correlates with the severity of ED [22]. In addition, 64% of men who presented with myocardial infarction had ED prior to their heart attacks, and 57% of men undergoing coronary artery bypass graft surgery had ED long before the operation [8].

ED has also been reported as an independent predictor of incident CAD [23]. Otherwise, ED often precedes CAD symptoms from other vascular beds; it is thought to be an early clinical manifestation of systemic atherosclerosis [24]. Greenstein et al. [25] found a relationship between ED and the presence of CAD, and there was a positive correlation between the severity of ED and the number of coronary vessels involved. The presence of coronary calcification, as measured by multislice computed tomography, is directly related to atherosclerotic diseases [26]. Chiurlia et al. showed that the presence and extent of calcification in the coronary arteries are greater in patients with ED [7].

Endothelial dysfunction is characterized by an imbalance between the endothelium-dependent vasodilator and vasoconstrictor activity, and is associated with a proinflammatory, proliferative, and procoagulatory milieu [27], all of which contribute to the mechanism of atherosclerosis [28]. Increasing evidence suggests that endothelial dysfunction is a systemic disorder, affecting both conduit arteries and microvessels in various vascular beds [29]. The key step that regulates endothelial function is endothelial-derived NO [27]. It is

synthesized from the conversion of L-arginine by endothelial NO synthase (eNOS) enzyme and is the key mediator of endothelium-dependent smooth muscle relaxation [30]. Impaired NO activity appears to play a key role in both endothelial dysfunction and ED [31]. The ability of the phosphodiesterase type-5 inhibitors to improve endothelial dysfunction and ED through the upregulation of NO confirms this hypothesis [32].

Giugliano et al. showed that the NO response in men with ED was lower than in men without it [33]. Elesber et al. measured a competitive inhibitor of NO synthase called asymmetric dimethylarginine to evaluate the presence of endothelial dysfunction among men with ED. In their study, the coronary vasoreactivity was evaluated by measuring dose responses to intracoronary adenosine boluses during coronary angiography. There was a statistically significant correlation between endothelial dysfunction, coronary vasoreactivity, and ED and asymmetric dimethylarginine levels [22].

Endothelial NO is important in producing the arterial and venous dilation necessary to attain and sustain an erection. Endothelial dysfunction is related to the loss of NO bioactivity in the endothelium [34]. Abnormalities of this vasodilator system are present in atherosclerosis and play an important role in the pathophysiology of ED [34]. The penile vascular bed is dependent on NO for vasodilatation of the arteries to produce rapid blood inflow and vasodilatation of the trabecular smooth muscle of the lacunar space to prevent venous outflow, making the penile vascular bed susceptible to deficiencies of the NO/cyclic guanosine monophosphate (cGMP) vasodilator system [34]. ED patients, who have undergone assessment of brachial arterial FMD and vasodilatation to the sublingual nitroglycerin, show peripheral vascular abnormality in the NO/cGMP pathway. FMD is known to be largely mediated by NO, suggesting that ED may be the first manifestation of cardiovascular disease caused by an abnormality in vascular NO/cGMP vasodilator system.

Rather than being thought of as a late consequence of a localized vascular disease, vasculogenic ED is now beginning to be considered an early manifestation of generalized vascular disease. Vasculogenic ED may result from impairment of endothelial-dependent and/or -independent smooth muscle relaxation (i.e., functional vascular ED, early stages), occlusion of the penile arteries by atherosclerosis (i.e., structural vascular ED, late stages), or a combination of these processes [35]. The small diameter of the cavernosal arteries and the relatively high content of endothelium and smooth muscle on a per-unit-volume tissue basis compared with other organs suggest that the penile vascular bed may be a sensitive indicator of systemic vascular disease [36]. From the pathophysiological viewpoint, endothelial dysfunction, as well as oxidative stress, is common denominators between ED and generalized vascular disease.

Reduced NO bioavailability is a cornerstone of the pathophysiology of ED. Dysfunctional endothelial cells lining the penile arterial system and the corpus cavernosum produce less NO. As a consequence, phosphodiesterase type 5, abundant in perivascular smooth muscle cells, degrades faster the reduced quantities of cGMP, thus limiting the duration of vasodilatation and having a negative impact on obtaining and sustaining an erection [37].

Endothelial dysfunction is not confined to penile tissue but is widespread in other vascular beds. Widespread endothelial dysfunction is further supported by additional findings. Circulating biochemical markers of endothelial cell activation, such as adhesion molecules and others, are found to be elevated in ED patients without risk factors and overt vascular damage [38]. Recent studies show that levels of asymmetric dimethylarginine, an endogenous competitive inhibitor of NOS, are increased in men with ED [39]. Furthermore, decreased numbers of circulating endothelial progenitor cells have been shown to be an independent predictor for ED [40].

The role of oxidative stress has been highlighted in vitro studies showing that increased production of reactive oxygen species is associated with decreased normal erectile response primarily because of inactivation of NO [37,41]. Oxidative stress and ox-LDL both alter endothelial biology by activating a specific receptor LOX-1. LOX-1 is expressed on the cell surface and can be proteolytically cleaved at its membrane proximal extracellular domain and released as sLOX-1 form, which can be measured in the serum [17]. The activation of LOX-1 has been shown to lead to further oxidative stress in endothelial cells and the appearance of proinflammatory phenotype [42]. Oxidative stress and subsequent inflammation have been characterized in several pathological processes including atherosclerosis from its beginning, such as the state of endothelial dysfunction, to its end sequelae, such as advanced atherosclerotic CAD [42]. Several studies have suggested that activation of the ox-LDL receptor

LOX-1 induces endothelial dysfunction, enhances ox-LDL uptake in monocytes/macrophages, and induces a state of oxidative stress. Accordingly, it has been suggested that LOX-1 is involved in the initiation and progression of endothelial dysfunction and atherosclerosis [43,44]. Activation of LOX-1 in endothelial cells induces the generation of superoxide, a reduction in the release of NO, and the expression of proatherogenic molecules such as endothelin-1, monocyte chemoattractant protein-1, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1 [13,45].

Deletion of LOX-1 in mice preserves endothelial function, leading to reduction in atherogenesis [44]. Activation of this receptor initiates intracellular signaling pathways leading to endothelial activation, dysfunction, and apoptosis [43]. Recent studies in animal and human tissues indicate that LOX-1 is upregulated in endothelial dysfunction and atherosclerotic lesions [46,47], and is involved in the reduction in protein kinase B, a key signaling pathway in eNOS expression [48].

Xu et al. [49] showed that increased expression of LOX-1, along with enhanced amounts of ox-LDL, induces endothelial dysfunction via activation of nicotinamide adenine dinucleotide phosphate-oxidase (NAD(P)H) oxidase and production of superoxide generation in atherosclerotic apolipoprotein E-knockout (ApoE KO) mice. Their findings were based on the following observations: antibody neutralization of LOX-1 prevented coronary endothelial dysfunction, reduced superoxide generation and expression of LOX-1, but increased protein expression of eNOS in ApoE KO mice. Their results showed a connection between the impaired dilation and LOX-1 in atherosclerosis because anti-LOX-1 prevented this impairment.

In conclusion, with the data of our study, we have shown a relationship between increased serum sLOX-1 and the presence and severity of ED, which may be postulated as evidence of endothelial dysfunction in ED. Serum sLOX-1 appears to be a specific predictor of ED, and for this reason, it may be used in early prediction of ED in male population. However, further clinical studies are needed to clarify the pathophysiological role of serum sLOX-1 in ED patients.

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