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Weight reduction can decrease circulating soluble lectin-like oxidized low-density lipoprotein receptor–1 levels in overweight middle-aged men

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Abstract

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–α ($r = 0.32$, $P = .09$); 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.

1. Introduction

Acute coronary syndrome (ACS) is one of the major causes of mortality and morbidity in developed countries. Because accurate diagnosis of ACS at the earliest stage can improve the prognosis of patients, a sensitive and specific early biomarker for ACS would be desirable. Moreover, oxidized low-density lipoprotein (Ox-LDL) and its receptor appear to play key roles in atherogenesis and the process of atherosclerotic plaque destabilization, erosion, and rupture, which are the major causes of ACS [1,2].

Lectin-like Ox-LDL receptor–1 (LOX-1), a type II membrane glycoprotein acting as a receptor for Ox-LDL, mediates Ox-LDL–induced vascular dysfunction [3-6]. Lectin-like Ox-LDL receptor–1 is cleaved from the cell surface by certain protease activities, released as soluble LOX-1 (sLOX-1). Circulating sLOX-1 levels are elevated in individuals with ACS, reflecting its prominent expression and enhanced protease activities in vulnerable atherosclerotic plaques in situ; and those circulating LOX-1 levels can be a useful biomarker for ACS [7,8]. Acute coronary syndrome is also thought to involve proinflammatory and immune responses [9,10]. Lubrano et al [11] have reported sLOX-1 as being associated with inflammatory markers. Obesity, on the other hand, can be characterized by a state of chronic low-grade inflammation [12,13]. Long-term activation of proinflammatory pathways may be a mechanism for the development of insulin resistance [14], whereas serum concentrations of various cytokines are increased in obese individuals and may decrease after weight reduction [15-17].

However, the pathophysiologic roles of sLOX-1 remain unclear. That is, the relationships between circulating sLOX-1 levels and inflammatory factors in obese individuals and the effect of weight reduction on circulating sLOX-1 levels are still unknown. Therefore, the aims of this study were (1)

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to assess whether weight reduction affects expression of sLOX-1 and (2) to assess whether changes in serum levels of sLOX-1 vary among individuals and whether they are associated with changes in anthropometric and metabolic parameters, adipocytokines, proinflammatory cytokines, and high-sensitivity C-reactive protein (hs-CRP) brought about by weight reduction in overweight middle-aged men.

2. Methods

2.1. Subjects

Thirty-eight Japanese men were recruited through advertisements in a local newspaper. Participants were excluded if they had a body mass index (BMI) less than 25 kg/m^2; were smokers; had concomitant renal, hepatic, or cardiac disease; and/or were being treated with drugs that could affect the variables of the study. Six subjects were unable to complete the study successfully for personal reasons. This left 32 men, aged 32 to 66 years, to be measured. Assays and measurements were carried out at 7 days before onset of the intervention and 10 days after a 12-week weight reduction intervention. The aim and design of the study were explained to all subjects before they gave their written consent. In addition, the study conformed to the principles outlined in the Helsinki Declaration and was approved by the Review Board of the University of Tsukuba.

2.2. Dietary and exercise protocol

All subjects were instructed to have a well-balanced 1680-kcal meal per day during the 12-week intervention. Subjects kept daily food diaries during this period and received weekly lectures and counseling from skilled dieticians. In addition to diet, subjects performed an exercise program that consisted of 36 walking and jogging sessions (3 d/wk), which were supervised by 2 or 3 exercise instructors. In the first 2 months, the exercise program entailed only walking, with the target Borg [18] scale ranging from 11 (light) to 13 (fairly hard). In the last month, subjects performed a combination of 3.0 km of brisk walking and 1.0 km of middle-intensity jogging, with the target Borg scale ranging from 13 (fairly hard) to 15 (hard). Subjects measured their heart rates by palpation while walking or jogging, and recorded the duration (minutes) and intensity (heart rate or the Borg scale) of each exercise session.

2.3. Clinical variables

Body weight was measured to the nearest 0.1 kg using a digital scale. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer, whereas BMI was calculated as weight (kilograms) divided by height squared (square meters). A dual-energy x-ray absorptiometry machine (DPX-NT; Lunar, Madison, WI) was used to evaluate body composition, which consisted of fat tissue and lean soft tissue. Visceral fat area (VFA) and subcutaneous fat area (SFA) were measured at the level of the umbilicus (L4-L5) using computed tomographic scans (Somatom AR.C; Siemens, Erlangen, Germany), which were performed on subjects in the supine position. The VFA and SFA were calculated using a computer software program (FatScan; N2system, Osaka, Japan). Systolic and diastolic blood pressures were measured with a sphygmomanometer, whereas maximal oxygen uptake (VO_2max) was determined during a graded exercise test using a cycle ergometer (828E; Monark, Stockholm, Sweden). After a 2-minute warm-up, subjects started with a workload of 30 W, which was increased by 15 W each minute until volitional exhaustion occurred. Pulmonary ventilation and gas exchange were measured breath-by-breath with an online data acquisition system (Oxycon Alpha System; Mijnhardt, Breda, Netherlands).

2.4. Blood analyses

A blood sample was drawn from each subject after a 12-hour fast. Serum glucose and lipids were assayed by routine automated laboratory methods, whereas hemoglobin A_{1c} was measured by ion-exchange high-performance liquid chromatography methods (Bio-Rad, Hercules, CA). Insulin was measured by an enzyme immunoassay method (Tosoh, Tokyo, Japan), and hs-CRP was measured by particle-enhanced immunoturbidimetric assay (Roche Diagnostics, Mannheim, Germany). Concentrations of serum LOX-1 were measured by a sandwich chemiluminescent enzyme-linked immunosorbent assay (ELISA) using 2 different human LOX-1–specific monoclonal antibodies with a recombinant human LOX-1 extracellular domain as an assay standard, which was modified from the previously described sandwich ELISA [19]. Monoclonal antibodies directed to human LOX-1 were established by standard hybridoma techniques after immunizing mice with a recombinant protein corresponding to the extracellular domain of human LOX-1. The serum leptin, tumor necrosis factor (TNF)–α, and interleukin (IL)-6 levels were measured with an ELISA kit (R&D Systems, Minneapolis, MN). The serum adiponectin levels were measured with an ELISA kit (Otsuka Pharmaceutical, Tokyo, Japan). Intra- and interassay coefficients of variation were 4.1% and 7.6% for LOX-1, 2.8% and 3.2% for leptin, 11.8% and 6.2% for TNF-α, 7.3% and 3.5% for IL-6, and 2.2% and 1.8% for adiponectin, respectively (n = 32).

2.5. Statistical analysis

Data were presented as mean ± standard deviation, and paired *t* tests were used to assess differences between variables before and after the weight reduction program. Relationships between 2 measurement variables were assessed by Pearson product moment correlation, whereas stepwise multiple regression analyses were used to estimate the independent contribution of the selected variables to the change in sLOX-1 concentration in response to weight

reduction. A value of $P < .05$ was considered to be statistically significant. All analyses were performed using SPSS software version 11.5 J for Windows (SPSS, Chicago, IL).

3. Results

Attendance at this intervention (36 sessions) averaged 80% (range, 50%-100%) for the subjects. The frequency of the exercise program was 2.4 ± 0.6 d/wk, with an average duration of 95 ± 27 min/wk.

As shown in Table 1, body weight, BMI, fat mass, percentage fat mass, serum lipid, and visceral fat decreased significantly; and VO_2max increased significantly. With the change in weight, serum sLOX-1 level decreased 72.1% ± 35.9%. There were only 2 subjects with slight increases in serum sLOX-1 level (Δ 1.1 pg/mL and Δ 6.6 pg/mL), while showing decreases in weight (Δ −10.3% and Δ −5.4%), fat mass (Δ −3.8% and Δ −11.0%), and VFA (Δ −43.8% and Δ−30.4%) (Fig. 1A and B).

As shown in Table 2, baseline serum sLOX-1 was positively correlated with baseline body weight ($r = 0.473$, $P = .01$) and BMI ($r = 0.453$, $P = .02$). Changes in sLOX-1 correlated positively with changes in body weight ($r = 0.542$, $P = .003$), BMI ($r = 0.574$, $P = .001$), and fat mass ($r = 0.570$, $P = .002$). No significant correlations were seen with fasting glycemic-related factors (blood glucose, hemoglobin A_{1c},

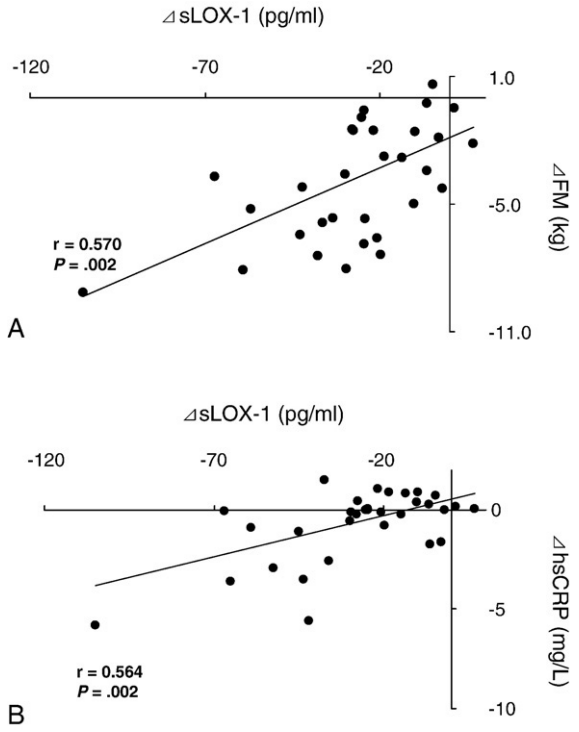

Fig. 1. Comparison of changes in serum LOX-1 levels with changes in fat mass and hs-CRP by simple linear regression analyses (n = 32). A, Δ sLOX-1 vs Δ fat mass. B, Δ sLOX-1 vs Δ hs-CRP. Serum sLOX-1 showed significant correlation with fat mass ($r = 0.570$, $P = .002$) and hs-CRP ($r = 0.564$, $P = .002$). Only 2 subjects showed slight increases in serum sLOX-1 levels. FM indicates fat mass.

Table 1
Subject characteristics at baseline and changes in measurements (n = 32)

	Baseline	Change	% Change
Age (y)	50.3 ± 12.4		
Body weight (kg)	75.4 ± 6.4	−7.5 ± 4.8	−9.9 ± 5.8‡
BMI (kg/m^2)	26.8 ± 2.2	−2.6 ± 1.7	−9.7 ± 6.0‡
Fat mass (kg)	18.9 ± 4.0	−3.6 ± 2.9	−19.0 ± 15.6‡
% Fat mass (%)	25.1 ± 4.6	−2.7 ± 2.8	−11.0 ± 12.8‡
VFA (cm^2)	168.1 ± 57.7	−57.2 ± 44.7	−34.2 ± 23.8‡
SFA (cm^2)	182.4 ± 56.9	−64.9 ± 37.6	−35.6 ± 18.1‡
Total fat area (cm^2)	350.4 ± 89.8	−122.1 ± 77.3	−34.2 ± 19.5‡
Systolic blood pressure (mm Hg)	131.1 ± 26.8	−9.3 ± 11.3	−6.5 ± 8.3‡
Diastolic blood pressure (mm Hg)	80.9 ± 17.5	−5.8 ± 8.6	−6.3 ± 10‡
TC (mg/dL)	216.2 ± 41.0	−13.5 ± 28.6	−6.2 ± 12.6*
HDLC (mg/dL)	55.6 ± 10.4	6.2 ± 10.1	11.2 ± 23.5†
LDLC (mg/dL)	134.0 ± 35.6	−10.8 ± 23.9	−8.1 ± 16.2*
Triglycerides (mg/dL)	132.2 ± 55.6	−44.8 ± 56.9	−33.8 ± 48.9‡
Fasting glucose (mg/dL)	96.1 ± 21.5	−2.3 ± 12	−1.2 ± 13.1
Insulin (μU/mL)	11.3 ± 2.7	−0.9 ± 6.1	−8.0 ± 14.6
Hemoglobin A_{1c} (%)	5.3 ± 1.1	−0.3 ± 0.5	−4.3 ± 7.9†
VO_2max (mL/[kg min])	29.3 ± 6.7	2.7 ± 4.6	9.6 ± 16.6†
sLOX-1 (pg/mL)	33.8 ± 24.7	−24.3 ± 23.2	−72.1 ± 35.9‡
hs-CRP (mg/L)	1.4 ± 1.8	−0.5 ± 1.7	−34.5 ± 110.0*
TNF-α (pg/mL)	0.7 ± 0.2	−0.1 ± 0.2	−10.1 ± 29.0*
IL-6 (pg/mL)	2.2 ± 1.5	−0.7 ± 1.5	−7.6 ± 76.3†
Leptin (ng/mL)	6.5 ± 4.4	−3.7 ± 4.0	−57.4 ± 4.8†
Adiponectin (μg/mL)	4.1 ± 1.5	1.8 ± 1.7	43.9 ± 40.8‡

Data are mean ± SD. Percentage change = change/baseline × 100. TC indicates total cholesterol; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol.

* $P < .05$.
† $P < .01$.
‡ $P < .001$.

Table 2
Correlation coefficients at baseline and changes in sLOX-1 (n = 32)

	Baseline	Change
Body weight (kg)	$r = 0.473$*	$r = 0.542$†
BMI (kg/m^2)	$r = 0.453$*	$r = 0.574$‡
Fat mass (kg)	$r = 0.343$	$r = 0.570$†
VFA (cm^2)	$r = -0.135$	$r = 0.252$
SFA (cm^2)	$r = 0.319$	$r = 0.498$†
TC (mg/dL)	$r = 0.275$	$r = 0.405$*
Triglycerides (mg/dL)	$r = 0.361$	$r = 0.219$
HDLC (mg/dL)	$r = -0.213$	$r = -0.254$
LDLC (mg/dL)	$r = 0.276$	$r = 0.489$†
Fasting glucose (mg/dL)	$r = -0.328$	$r = 0.097$
Hemoglobin A_{1c} (%)	$r = -0.281$	$r = 0.022$
VO_2max (mL/[kg min])	$r = 0.053$	$r = -0.129$
hs-CRP (mg/L)	$r = 0.575$‡	$r = 0.564$†
TNF-α (pg/mL)	$r = 0.263$	$r = 0.321$
IL-6 (pg/mL)	$r = 0.146$	$r = 0.196$
Leptin (ng/mL)	$r = 0.421$*	$r = 0.468$*
Adiponectin (μg/mL)	$r = -0.177$	$r = 0.176$

* $P < .05$.
† $P < .01$.
‡ $P < .001$.

Table 3
Stepwise multiple regression analysis for change in sLOX-1 (n= 32)

Independent variable	β	P	Change in R^2 (%)
Δ BMI	.574	.001	30.4
Δ hs-CRP	.128	.006	15.5

and insulin) and VO_2max at baseline or with changes. Correlations in changes in sLOX-1 with changes in BMI (r = 0.437, P = .023) and fat mass (r = 0.462, P = .015) were significant even after adjustment for body weight.

High-sensitivity CRP, TNF-α, IL-6, leptin, and adiponectin decreased significantly (Table 1). Baseline sLOX-1 was positively correlated with baseline hs-CRP (r = 0.58, P = .001), whereas changes in sLOX-1 correlated positively with hs-CRP (r = 0.56, P = .002). These associations remained significant after adjustment for body weight. Changes in sLOX-1 correlated positively with leptin (r = 0.47, P = .01) and TNF-α (r = 0.32, P = .09) (Table 2). Stepwise multiple regression analysis indicated that changes in BMI and hs-CRP were significant predictors of change in sLOX-1 (R^2 = 0.459), as shown in Table 3.

4. Discussion

Proteolytic cleavage of LOX-1 releases a soluble form of the receptor. Because the level of soluble receptors in circulating blood may reflect expression of membrane proteins and disease activities, sLOX-1 may be a potential biomarker of vascular disease and ACS [20,21]. Brinkley et al [22] have reported that LOX-1 polymorphisms may be associated with plasma sLOX-1 levels.

In the current study, the following 3 findings were obtained: First, serum sLOX-1 levels decreased significantly with weight reduction. Second, basal serum sLOX-1 levels correlated positively with basal body weight and BMI. Changes in serum sLOX levels correlated positively with changes in body weight, BMI, fat mass, abdominal fat area, and serum lipid; but no significant correlations were observed with glycemic-related factors and VO_2max. Third, changes in sLOX-1 levels were positively correlated with changes in hs-CRP and leptin. They were also marginally correlated with TNF-α, whereas no correlations were observed with IL-6. Changes in BMI and hs-CRP were significant predictors for change in sLOX-1 concentration.

According to our observations, weight reduction contributed not only to lowering circulating sLOX-1 levels but also to reducing fat mass, abdominal fat area, and serum lipids, all of which are well-known risk factors for vascular disease. Changes in sLOX-1 levels were also significantly correlated with changes in the factors mentioned above. These results suggest that LOX-1 expression may be related to adipocyte metabolism. Brinkley et al [23] reported that plasma levels of sLOX-1 were significantly correlated with body weight, BMI, and total body fat. Although their study may be the first to report an interaction between serum sLOX-1 levels and obesity, it supports our data here.

Obesity is also associated with alterations in immune function, but the effect of obesity itself on immune system function is variable [24]. Obese subjects seem to primarily have impairment in immune response that is reversible with weight reduction [14,15]. Serum sLOX-1 level increased because LOX-1 can be induced by proinflammatory stimuli [11,25]. Indeed, Honjo et al [26] found that LOX-1 is involved in endotoxin-induced inflammation as well as leukocyte recruitment and infiltration in vivo; and these studies suggest that LOX-1 plays a role in inflammation and immune response. Our observations indicated that hs-CRP, TNF-α, IL-6, and leptin were significantly reduced, as was sLOX-1, and that changes in sLOX-1 were correlated with hs-CRP and TNF-α. From these results, we speculate that inflammatory conditions were ameliorated by weight reduction. It follows that circulating sLOX-1 decreased. The LOX-1 induction may therefore be associated with inflammation and immune response.

Recent reports [27-29] indicate that the basal expression of LOX-1 in endothelial cells is very low. However, it can be rapidly induced by proinflammatory, prooxidant, and mechanical stimuli such as Ox-LDL [27], TNF-α [25], hs-CRP [28], and shear stress [29]. Lectin-like Ox-LDL receptor–1 binding to Ox-LDL rapidly elevates reactive oxygen species levels including superoxide anion and hydrogen peroxide via a membrane-bound nicotinamide adenine dinucleotide phosphate oxidase. Reactive oxygen species can activate 2 signal transduction pathways involving either P38 mitogen-activated protein kinase or phosphoinositide 3-kinase, with both causing nuclear factor–κB activation and enabling nuclear translocation and subsequent regulation of proinflammatory gene expression [30-33]. According to our study, in which changes in serum sLOX-1 levels were correlated with hs-CRP and TNF-α, circulating sLOX-1 levels may be the result of hs-CRP and TNF-α activating LOX-1 via the nuclear factor–κB system. Two subjects showed slight increases in serum sLOX-1 levels; and their basal levels of sLOX-1 (7.1 and 11.0 pg/mL), hs-CRP (0.5 and 0.7 mg/L), and TNF-α (0.1 and 0.2 pg/mL) were very low. Thus, these data may support this phenomenon.

Two limitations of this study were the small sample size and the fact that subjects were composed solely of middle-aged Japanese men. Future research should therefore make use of a wider range of subjects in terms of age, sex, and race. Nevertheless, this is the first study to examine whether serum sLOX-1 level can be related to weight reduction in overweight individuals. Further studies are needed to clarify the clinical evidence for sLOX-1 being useful as an early biomarker for ACS.

In conclusion, serum sLOX-1 level was significantly reduced via weight reduction intervention in middle-aged men. It was also significantly correlated with changes in BMI, fat mass, abdominal fat area, serum lipids, leptin, hs-

CRP, and TNF-α. These results suggest that LOX-1 induction may be related to adipocyte metabolism, inflammation, and immune response.

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