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ORIGINAL ARTICLE

Pitavastatin Reduces Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1 Ligands in Hypercholesterolemic Humans

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Abstract 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

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levels of LOX-1 ligand may be a useful biomarker of the pleiotropic effects of statins.

Keywords Pitavastatin · Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) · Pleiotropic effects

Abbreviations

LOX-1	Lectin-like oxidized LDL receptor-1
sLOX-1	Soluble LOX-1
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
OxLDL	Oxidized low-density lipoprotein
CRP	C-reactive protein
ELISA	Enzyme-linked immunosorbent assay
TAG	Triacylglycerol
TC	Total cholesterol

Introduction

Numerous clinical studies on statin therapy have demonstrated that a reduction in plasma levels of low-density lipoprotein cholesterol (LDL-C) prevents atherosclerotic progression and decreases cardiovascular risk [1–3]. There is a growing body of evidence that the oxidative modification of LDL is involved in the progression of atherosclerosis. It has been reported that plasma levels of oxidized LDL (OxLDL) were elevated in patients with coronary artery disease, and were associated with plaque instability in coronary artery disease [4, 5]. However, the clinical study of LDL oxidation has been hampered by the difficulty of a specific assay for plasma levels of OxLDL. It has been shown that statins reduce the production of reactive oxygen species through pleiotropic effects independent of cholesterol reduction [6–8]. The effects of statins on various circulating biomarkers of oxidative stress have been reported in clinical studies.

Lectin-like OxLDL receptor-1 (LOX-1) is a receptor for OxLDL that is mainly expressed in vascular endothelial cells, and OxLDL uptake through this receptor may be involved in endothelial dysfunction in atherogenesis [9, 10]. More recently, a novel sandwich enzyme immunoassay for LOX-1-ligand, which uses a recombinant soluble form of LOX-1 and anti-apoB antibody, has been developed to detect circulating modified LDL via specific binding to LOX-1 [11].

Pitavastatin is a strong statin similar to atorvastatin and rosuvastatin [12–14], and has been shown to have pleiotropic effects in vitro. To date, there have been no reports on the relations between the effects of pitavastatin on LDL levels and LDL oxidation in humans. Thus, we examined the effects of pitavastatin on serum levels of LOX-1 ligand activity and soluble LOX-1 (sLOX-1), and their relationships in patients with hypercholesterolemia.

Methods

Study Patients

Twenty-five subjects, between the ages of 21 and 80 years, with a baseline LDL-C between 160 and 220 mg/dL who were not receiving lipid-lowering therapy were recruited. Exclusion criteria included exposure to cholesterol-reducing drugs within the previous 6 weeks, coronary artery disease, congestive heart failure, significant renal or hepatic disease, familial hypercholesterolemia, and pregnant or lactating women.

Protocol

After informed consent was obtained from all participants before the study, pitavastatin was administered at a dose of 2 mg/day for 6 months. Data obtained before and after 6 months of treatment with pitavastatin included fasting blood work, adverse events, and the results of a physical examination. Laboratory analyses of blood work included lipid analyses and the assessment of other biomarkers. All assays were carried out by personnel who did not know the clinical characteristics of the patients.

Measurement of Biomarkers

Blood samples for measuring the plasma or serum concentrations of parameters were collected from the peripheral vein at the time of the patient visit. The blood samples were immediately placed on ice and centrifuged at −30 °C until assay.

Lipid parameters [total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), and triacylglycerol (TAG)] were analyzed from ethylenediaminetetraacetic acid-treated plasma, and determined by commercially available enzymatic-colorimetric methods. Serum levels of high-sensitivity CRP were determined by a sensitive nephelometric assay (Dade, Behring, Japan). Fasting blood sugar, hemoglobin A1c, creatinine, uric acid, and creatine kinase, and a liver function test were measured by standard techniques.

Measurement of sLOX-1

According to a previous report [15], serum sLOX-1 levels were determined by a sandwich ELISA. Forty microliter of

standard recombinant human LOX-1 (61-273) or fourfold-diluted sera were applied to 384-well plates immobilizing anti-human LOX-1 antibody (TS92, 0.25 μg/well) [9]. Bound sLOX-1 was detected by the combination of another anti-human LOX-1 antibody (HUC5-40) and a peroxidase-conjugated donkey anti-chicken IgY (AP194P, Chemicon, MA) with TMB solution.

Measurement of LOX-1 Ligand Activity

LOX-1 ligand activities in plasma were determined according to a previous report [11]. Recombinant LOX-1 (0.4 μg/well) was immobilized on 96-well plates (Maxisorp, Nunc) by incubating overnight at 4 °C in 50 μL of PBS. After being washed twice with PBS, the plates were blocked with 0.3 mL of 20% (v/v) ImmunoBlock (DS Pharma) for 8 h at 4 °C. After being washed three times with PBS, the plates were incubated with 0.1 mL of the standard OxLDL or plasma diluted 40-fold with EDTA–HEPES buffer [10 mM HEPES (pH 7.0), 150 mM NaCl, 2 mM EDTA]. The plates were then washed three times with PBS, and incubated for 1 h at room temperature with 0.5 μg/mL HUC20, a chicken monoclonal antibody that recognizes mouse and human ApoB, in PBS containing 1% (w/v) BSA. After being washed three times with PBS, the plates were incubated for 1 h at room temperature with peroxidase-conjugated goat anti-chicken IgG (H + L) (KPL, Gaithersburg, MD) diluted 2,000-fold with PBS containing 1% (w/v) BSA. After being washed five times with PBS, a substrate solution containing 3,3′, 5,5′-tetramethylbenzidine (TMB solution, Bio-Rad Laboratories, Hercules, CA) was added to the plates and incubated at room temperature for 30 min. The reaction was terminated by the addition of 50 μL of 2 M sulfuric acid. Peroxidase activity was determined by the measurement of absorbance at 450 nm.

Statistical Analysis

Data are expressed as the mean values ± SD. To analyze the effects of treatment with pitavastatin for 6 months, the paired Student's *t* test was applied to paired data. Linear regression analyses were carried out to detect correlations between continuous valuables. A value of $P < 0.05$ was considered statistically significant.

Results

Subject Characteristics

The characteristics of the study population are shown in Table 1. The mean age of the study population was 63 ± 13 years and most of the subjects were female (68%). The subjects enrolled in this study had hypertension ($n = 16$, 64%) and diabetes mellitus ($n = 1$, 4%). Similar medical treatments were continued throughout the study period. Systolic and diastolic arterial pressures and pulse rate did not change during the study period (Table 1). All subjects completed the 6-month study protocol without any adverse side effects, and no clinical disorder developed during the study period.

Effects of Pitavastatin on Biochemical Profiles

Table 1 shows the lipid parameters before and after pitavastatin treatment. Before pitavastatin treatment, TC and LDL-C levels were abnormally high (268 ± 26 and 182 ± 21 mg/dL, respectively). TC (268 ± 26 vs. 176 ± 17 mg/dL) and LDL-C (182 ± 21 vs. 96 ± 14 mg/dL) significantly decreased after pitavastatin treatment ($P < 0.0001$ for each) (Table 1; Fig. 1a). Although pitavastatin treatment significantly decreased TAG from 145 ± 65 to 104 ± 40 mg/dL ($P < 0.0001$), it did not significantly change HDL-C (before, 57 ± 14 mg/dL; after, 58 ± 15 mg/dL; P = ns) (Table 1). Fasting blood sugar, hemoglobin A1c, uric acid, and creatinine phosphokinase were unchanged during the study period (Table 1). Other biochemical markers including liver function were unchanged (data not shown).

Measurement of LDL Ligands, sLOX-1, and High-Sensitivity CRP

LOX-1 ligands remarkably decreased with pitavastatin treatment (867 ± 452 vs. 435 ± 262 ng/mL, $P < 0.0001$)

Table 1 Hemodynamic and biochemical parameters before and after pitavastatin treatment

	Before	After	
Systolic BP (mmHg)	136 ± 20	123 ± 16	ns
Diastolic BP (mmHg)	78 ± 15	69 ± 9	ns
Pulse rate (/min)	71 ± 11	72 ± 12	ns
Total cholesterol (mg/dL)	268 ± 26	176 ± 17	$P < 0.0001$
LDL-cholesterol (mg/dL)	182 ± 21	96 ± 14	$P < 0.0001$
HDL-cholesterol (mg/dL)	57 ± 14	58 ± 15	ns
Triglyceride (mg/dL)	145 ± 65	104 ± 40	$P < 0.0001$
FBS (mg/dL)	108 ± 30	104 ± 20	ns
Hemoglobin A1c (%)	5.6 ± 0.4	5.6 ± 0.5	ns
CK (IU/L)	117 ± 57	162 ± 99	ns
Uric acid (mg/dL)	5.9 ± 2.0	5.6 ± 1.5	ns
Creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.2	ns

Values are means ± SD

BP blood pressure, *FBS* fasting blood sugar, *CK* creatine kinase

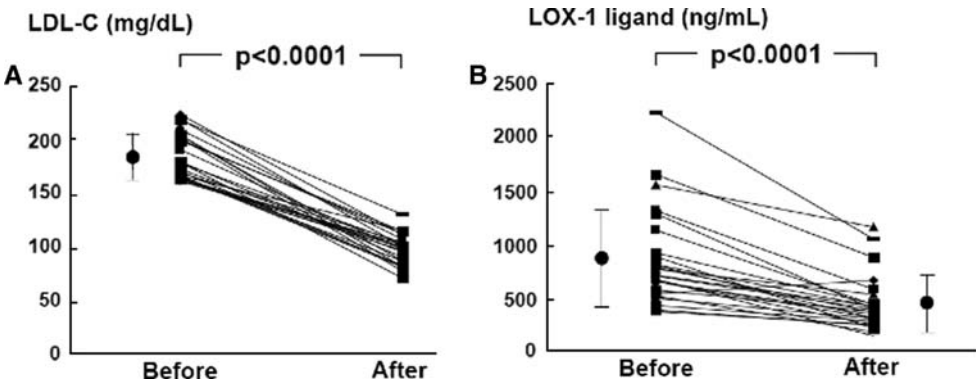

Fig. 1 Levels of low-density lipoprotein cholesterol (LDL-C) (**a**) and lectin-like oxidized LDL receptor-1 (LOX-1) ligand (**b**) before and after 6 months of treatment with pitavastatin

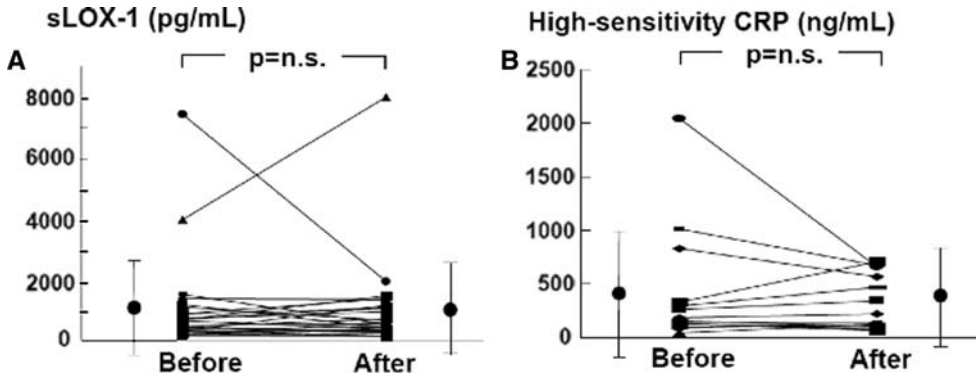

Fig. 2 Levels of soluble LOX-1 (sLOX-1) (**a**) and high-sensitivity CRP (**b**) before and after 6 months of treatment with pitavastatin

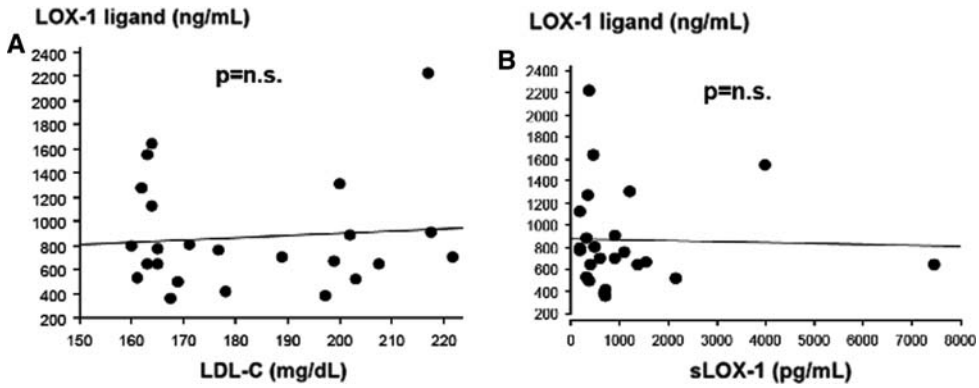

Fig. 3 Relationship between LOX-1 ligands and LDL-C before pitavastatin treatment (**a**). Relationship between LOX-1 ligands and sLOX-1 before pitavastatin treatment (**b**)

(Fig. 1b). Meanwhile, soluble LOX-1 (1,059 ± 1,530 vs. 1,022 ± 1,526 pg/mL) (Fig. 2a) and high-sensitivity CRP (0.42 ± 0.59 vs. 0.39 ± 0.45 mg/L) (Fig. 2b) did not change with pitavastatin treatment. In a 73-year-old woman with hypertension and stable angina pectoris, a marked increase in soluble LOX-1 levels was observed after treatment with pitavastatin (3,980–8,010 pg/mL). Her clinical characteristics and medical treatments did not change during the study period.

Before pitavastatin treatment, there was no significant linear correlation between LOX-1 ligands and LDL-C (Fig. 3a), or between LOX-1 ligands and sLOX-1 (Fig. 3b). In two subjects, basal sLOX-1 levels were far higher (>3,000 pg/mL) than those in the other 22 subjects. In the remaining 22 subjects, the degree of the reduction in LOX-1 ligands correlated with that in sLOX-1 (Fig. 4a), but not that in LOX-1 ligands (Fig. 4b).

Discussion

We first demonstrated that treatment with pitavastatin reduced LOX-1 ligands as well as TC, LDL-C, and TAG in hypercholesterolemic patients. The measurement of LOX-1 ligands may be useful as a tool for estimating pleiotropic effects of statins.

Statin therapy can ameliorate future cardiovascular events, and this improvement has been ascribed not only to

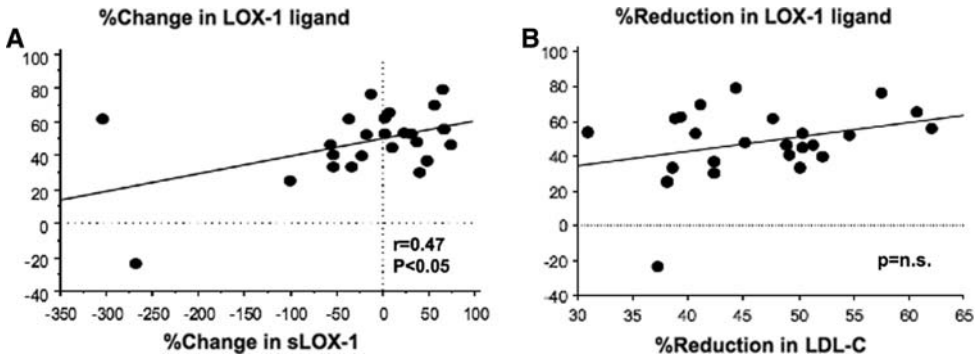

Fig. 4 Relationship between the degree of reduction in LOX-1 ligands and that in sLOX-1 (**a**). Relationship between the degree of reduction in LOX-1 ligands and that in LDL-C (**b**)

reductions in LDL cholesterol but also to the antioxidant properties of statins [6, 8, 16]. Different statins have different antioxidative capacities for LDL oxidation, and it is speculated that pitavastatin hinders the development of atherosclerosis by reducing the oxidative modification of LDL.

OxLDL is implicated in endothelial dysfunction as well as the formation and progression of atherosclerosis [10, 17]. It has been shown that plasma levels of OxLDL were elevated in patients with coronary artery disease, and were associated with the severity of acute coronary syndrome and coronary artery disease [4, 5]. We previously reported that plasma levels of OxLDL were a useful measure of coronary endothelial dysfunction [18]. However, the clinical importance of circulating OxLDL has not yet been fully elucidated.

Several receptors for OxLDL have been identified over the past few years [19–21]. LOX-1 is one such receptor for OxLDL and is expressed in atherosclerotic lesions, including endothelial cells, macrophages, and smooth muscle cells [9, 22]. OxLDL binds to LOX-1, resulting in NADPH oxidase activation and eNOS downregulation, and the atherogenic properties induced by OxLDL are mainly mediated via LOX-1 [10]. LOX-1 can be cleaved at its membrane proximal extracellular domain and released as soluble forms of LOX-1 [23]. It has been reported that serum levels of sLOX-1 are elevated in coronary artery disease [24, 25]. In the present study, soluble LOX-1 did not change after pitavastatin treatment. The expression of LOX-1 could be enhanced by risk factors for atherosclerosis such as hyperlipidemia, hypertension, and diabetes mellitus [22]. In the present study, arterial pressures and biochemical profiles other than lipid levels remained unchanged during the study.

LOX-1 recognizes multiple ligands such as OxLDL, apoptotic cells, bacteria, and platelets [10, 22]. The precise OxLDL epitope recognized by LOX-1 is not known. OxLDL is not one homogeneous entity, but rather represents multiple chemical and immunogenic modifications of the lipid and apoB-100 on LDL. ApoB-containing lipoproteins and their oxidized form play an important role in the pathogenesis of atherosclerosis. We previously demonstrated that plasma levels of LOX-1 ligands were increased in ApoE-deficient mice fed a high-fat diet and there was a link between the level of LOX-1 ligands and the progression of atherosclerosis in mice [11]. Recently, LOX ligands have been shown to be associated with the incidence of cardiovascular disease [15].

In the present study, we showed that pitavastatin can reduce LOX-1 ligands but not sLOX-1. Circulating levels of sLOX-1 may not change after pitavastatin treatment, although the vascular expression of LOX-1 was decreased with pitavastatin treatment. As for pitavastatin, the reduction in LOX-1 ligand levels was similar to that in LDL-cholesterol levels. The changes in LOX-1 ligands were correlated with those in sLOX-1, suggesting a potent link between sLOX-1 and LOX-1 ligands. Before pitavastatin treatment, LOX-1 ligands showed no significant correlation with plasma LDL-C levels. In addition, the degree of the reduction in LOX-1 ligands was not significantly correlated with that in LDL-C levels. Numerous trials have shown that statins can lower LDL-C levels. In addition, LOX-1 ligand levels may be a suitable biomarker for estimating the pleiotropic effects independent of the cholesterol-lowering effects of statins. In previous studies using WHHL rabbits, fluvastatin significantly reduced plasma levels of both LOX-1 ligands and TC, as well as the atherosclerotic lesion area and the cholesterol content of aortic arches [26].

In the present study, treatment with pitavastatin did not change plasma levels of CRP. CRP is produced predominantly in the liver as part of the acute-phase response, and is also expressed in smooth muscle cells within diseased atherosclerotic arteries [27]. CRP and LOX-1 share a range of biological functions. CRP can induce LOX-1 expression [28], and the binding of CRP to LOX-1 enhances the binding affinity of OxLDL to LOX-1 [29]. Statin therapy reduces high-sensitivity CRP by a mechanism beyond LDL reduction [14]. Koshiyama et al. [30] reported that pitavastatin lowered high-sensitivity CRP in patients with hypercholesterolemia. Our modest sample size might have limited the observed effects of pitavastatin on serum high-sensitivity CRP levels. Further studies are needed to

address whether serum levels of LOX-1 ligands are associated with anti-inflammatory, anti-thrombotic, and vascular endothelial effects.

In conclusion, pitavastatin therapy reduces both LDL-C and LOX-1 ligands in hypercholesterolemic subjects. Serum levels of LOX-1 ligands may be a useful biomarker for monitoring the pleiotropic effects of statins, and the reduction of LOX-1 ligands by statins, other antioxidants, or lifestyle modifications may be a promising therapeutic strategy against atherosclerosis and future cardiovascular events.

Study Limitations

Several important questions remain regarding the impact of pitavastatin on LOX-1 in hypercholesterolemic subjects. For example, our findings are limited by the fact that this was an uncontrolled study with a modest number of subjects. Furthermore, we did not address the question of the dose–response effects of pitavastatin on LOX-1. We must validate our findings in randomized, well-controlled and larger human studies. In addition, further analyses must be performed to examine whether patients with risk factors for atherosclerosis have higher levels of LOX-1 ligand activity than healthy subjects.

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Conflict of interest statement We have no any commercial associations that might pose a conflict of interest in connection with this article.

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