Mechanisms of High-Density Lipoprotein Cholesterol Effects on the Endothelial Function in Hyperlipemia

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High-density lipoprotein-cholesterol (HDL-c) has a favorable influence on the endothelial function, but the mechanisms of this protective action are not fully understood. We studied lipid parameters, soluble adhesion molecules (vascular cell adhesion molecule-1 [VCAM-1], intercellular adhesion molecule [ICAM-1], E-selectin) oxidized low-density lipoproteins (LDL), and brachial-artery flow-mediated vasodilation (FMV) in 184 hyperlipemic patients (90 men, age 54 ± 10 years, waist/hip circumference ratio 0.89 ± 0.07, LDL-cholesterol [LDL-c] 4.9 ± 1.3 mmol/L, triglycerides 1.8 ± 0.9 mmol/L, HDL-c 1.3 ± 0.5 mmol/L) after excluding those with current smoking, diabetes, hypertension, and vascular diseases. Patients were divided into 2 groups on the basis of HDL-c levels: < 1.03 mmol/L (n = 53) *v* ≥ 1.03 mmol/L (n = 131). Patients with low HDL-c showed significantly lower LDL-c (*P* < .05), higher triglycerides (*P* < .001), higher body mass index (*P* < .02), lower FMV (3.7% ± 2.0% *v* 4.9% ± 3.4%, *P* < .002), higher VCAM-1 (1,195 ± 395 ng/mL *v* 984 ± 303 ng/mL, *P* < .01), and higher ICAM-1 (406 ± 78 ng/mL *v* 364 ± 68 ng/mL, *P* < .01). E-selectin and oxidized LDL showed no significant differences. In a multivariate age, oxidized LDL and brachial artery diameter predicted a lower FMV, while HDL-c was an independent predictor of a greater FMV (*P* = .003). Increasing levels of VCAM-1 and ICAM-1 were predicted by lower HDL-c, while higher oxidized LDL predicted higher VCAM-1 (*P* < .05). Our data suggest that in hyperlipemic subjects free of cardiovascular disease low HDL-c negatively modulates endothelial function through a lack of oxidation inhibition and a concomitant overexpression of adhesion molecules.

HIGH-DENSITY lipoprotein-cholesterol (HDL-c) exerts a powerful favorable action on atherosclerotic disease.[1-2] Beyond the well-known HDL-mediated reverse cholesterol transport,[3] several mechanisms have been hypothesized to underlie the beneficial vascular effects of HDL-c. First, an altered endothelial reactivity to a number of physical and chemical stimuli is considered the first stage of atherosclerosis,[4] and HDL-c has been shown to exert a favorable effect on endothelial reactivity both in healthy subjects[5] and in hyperlipemic patients.[6] Secondly, HDL-c is able to modulate the expression of cell adhesion molecules in the early stages of the atherogenetic process.[7] Vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin, which can be detected in plasma as soluble forms, mediate the adhesion of leukocytes to the endothelium and their subsequent transmigration into the intima,[7] and their plasma concentration is considered a marker of endothelial dysfunction. The expression of soluble cell adhesion molecules is enhanced by several vascular risk factors, including hypercholesterolemia, hypertriglyceridemia, and increased levels of small dense low-density lipoproteins (LDL).[8,9] Cell adhesion molecules are also increased in subjects with low HDL-c levels, raising the possibility that the increased expression of cell adhesion molecules may be one link between low HDL-c and atherosclerosis.[10] Third, several in vitro and in vivo studies suggest that HDL may also influence the atherogenic process by antagonizing LDL oxidation, thus reducing oxidative changes of the LDL.[11-13]

In the present study, we aimed at investigating the mechanisms of HDL protection in vivo on endothelial function in hyperlipemic patients. In particular, we determined soluble adhesion molecules, oxidized LDL and brachial-artery flow-mediated vasodilation (FMV), a noninvasive measure of endothelial function, in a population of hyperlipemic subjects free of cardiovascular disease. A second aim of our study was to investigate whether a relationship exists in vivo between an ultrasound and a biochemical marker of endothelial dysfunction.

MATERIALS AND METHODS

Subjects

We examined 184 hyperlipemic patients of both genders, aged 30 to 68 years, referred to our Lipid Clinic with a diagnosis of primary hyperlipemia. Inclusion criteria were LDL cholesterol ≥ 4.13 mmol/L and/or triglycerides ≥ 2.25 mmol/L. All subjects underwent clinical examination, ultrasonographic assessment of brachial artery FMV, and determination of serum lipids, oxidized LDL and soluble VCAM-1, ICAM-1, and E-selectin.

Only patients with stable HDL-c levels were included in the study; patients whose HDL-c values obtained in the previous 6 months differed by ≥ 10% from the last value were excluded from the study. We also excluded all patients with conditions known to affect endothelial function, including cigarette smoking, diabetes mellitus (fasting glycemia >126 mg/dL), blood pressure >160/95 mm Hg, history or clinical evidence of ischemic heart disease, peripheral artery disease, cerebrovascular disease, and current therapy with antiplatelet, hypolipemic, antioxidant, and antihypertensive drugs or hormone replacement treatment. Other exclusion criteria were recent infectious diseases, connec-

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Table 1. Clinical Characteristics of Subjects With HDL-C Below and Above 1.03 mmol/L

	HDL-c < 1.03 mmol/L (<40 mg/dL) (n = 53)	HDL-c ≥ 1.03 mmol/L (≥40 mg/dL) (n = 131)	*P*
Age (yr)	51.8 ± 9	55.4 ± 10	.025
Men (%)	75	38	<.001
Body mass index (kg × m^{-2})	26.4 ± 2.8	25.3 ± 3.1	.021
Waist-hip circumference ratio	0.90 ± 0.1	0.88 ± 0.1	NS
Systolic blood pressure (mm Hg)	131 ± 12	130 ± 12	NS
Diastolic blood pressure (mm Hg)	80 ± 7	77 ± 9	.015
LDL cholesterol mmol/L [mg/dL]	4.60 ± 1.4 [178.1 ± 54.1]	5.06 ± 1.1 [195.8 ± 44.9]	.049
HDL cholesterol mmol/L [mg/dL]	0.81 ± 0.1 [31.3 ± 3.9]	1.52 ± 0.4 [58.8 ± 15.5]	<.001
Triglycerides mmol/L [mg/dL]	2.31 ± 1.0 [207.3 ± 88.7]	1.54 ± 0.7 [136.6 ± 62.0]	<.001
Oxidized LDL (U/L)	79 ± 35	73 ± 27	NS
VCAM-1 (ng/mL)	1195 ± 395	984 ± 303	<.001
ICAM-1 (ng/mL)	406 ± 78	364 ± 68	.003
E-selectin (ng/mL)	35 ± 15	33 ± 15	NS
Brachial artery diameter (mm)	4.19 ± 0.7	3.95 ± 0.7	.04
Posthyperemic diameter (mm)	4.3 ± 0.7	4.1 ± 0.7	N.S.
Flow-mediated vasodilation (%)	3.7 ± 2.0	4.9 ± 3.4	.003
Baseline blood flow (mL × min^{-1})	120 ± 36	133 ± 36	NS
Posthyperemia blood flow (mL × min^{-1})	298 ± 21	301 ± 37	NS

NOTE. Data are presented as mean (SD).

Abbreviations: LDL, low-density lipoprotein; HDL-c, high-density lipoprotein cholesterol VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; NS, not significant.

tive tissue disease, neoplasms, congestive heart failure, renal, or liver insufficiency.

Procedures

Blood was drawn in the morning after a 13-hour fast. The following parameters were determined: total cholesterol, triglycerides (enzymatic colorimetric method), HDL-c (enzymatic colorimetric method after precipitation with polyethilenglycole). Triglyceride concentration was ≤ 4.52 mmol/L in all subjects, thus LDL cholesterol was calculated from the Friedewald equation.[14] Levels of oxidized LDL were measured by an enzyme-linked immunosorbent assay (ELISA) direct sandwich technique in which 2 monoclonal antibodies are directed against separate antigenic determinants on the oxidized apoprotein B molecule (Marcodia, Uppsala, Sweden) in frozen plasma of all subjects. The assays were performed in duplicate for each sample. Intra-assay and interassay precisions (coefficient of variation) for all of these assays were < 8%, and < 12%, respectively.

Levels of sICAM-1, sVCAM-1, and sE-Selectin were determined by the use of monoclonal antibody-based ELISA assays (CHEMICON International, Temecula, CA) on frozen serum from all subjects. The assays were performed in duplicate for each sample. Concentrations of samples were determined by analyzing standards with known concentrations of recombinant adhesion molecules coincident with samples and plotting a curve of signal versus concentration. A control sample of known sICAM-1, sVCAM-1, and sE-selectin concentrations was performed with each assay. If the values were not within the expected range of this control, the assay results were invalid. Intra-assay and interassay precisions (coefficient of variation) for all of these assays were < 4.1% and < 7.7%, respectively, as reported by the manufacturers.

FMV was assessed under fasting conditions between 8 AM and 10 AM by 2-dimensional ultrasonography of the brachial artery using a 10-MHz probe (AU4; ESAOTE, Florence, Italy), as previously reported in detail[15] according to the guidelines of the International Brachial Artery Reactivity Task Force.[16] Briefly, FMV was expressed as the percent difference between the brachial artery diameter measured 45 to 60 seconds after a 4-minute upper arm occlusion by a pneumatic cuff at 230 to 250 mm Hg and the baseline diameter. The intra-observer between-occasion difference in FMV, assessed in 21 subjects examined 2 days apart, was 1.0% ± 1.5%.

To assess endothelium-independent vasodilation, spray nitroglycerin, 0.4 mg, was given sublingually to a subgroup of hypercholesterolemic patients, 7 with HDL-c below 1.03 mmol/L, and 10 with HDL-c ≥ 1.03 mmol/L. Brachial artery diameter was measured before and 4 minutes after the drug administration.

Statistical Analysis

To analyze the influence of HDL-c on the examined variables, patients were divided into 2 groups on the basis of HDL-c levels (<1.03 mmol/L *v* ≥ 1.03 mmol/L). Statistical testing of differences in continuous variables between groups was made by Student's unpaired *t* test for normally distributed variables and by Mann-Whitney *U* test for triglycerides, body mass index, and waist/hip ratio. Spearman's rank correlation coefficients tested the relationship between FMV and several demographic, clinical, and biochemical variables. Multiple linear regression analysis assessed the independent contribution to FMV and to VCAM-1 and ICAM-1 of several variables including age, sex, body mass index, diastolic blood pressure, HDL-c, triglycerides, and brachial artery diameter (this last one only for FMV).

RESULTS

Table 1 shows several clinical and biochemical parameters in the 2 groups. Patients with low HDL-c were more frequently men and had higher diastolic blood pressure, body mass index, and serum triglycerides. LDL cholesterol was higher in subjects with higher levels of HDL-c, while the 2 groups did not differ in terms of oxidized LDL. FMV was significantly lower in subjects with low HDL-c (3.7% ± 2.0% *v* 4.9% ± 3.4%, *P* <

.001). Both VCAM-1 and ICAM-1 levels were significantly higher in subjects with low HDL-c.

Endothelium-independent vasodilation was 9.7% ± 1.0% in the subgroup with low HDL-c and 10.1% ± 0.9% in the subgroup with higher HDL-c.

In the univariate correlations, FMV had a significant direct association with HDL-c ($r = .26$, $P < .001$) and an inverse one with LDL cholesterol ($r = -.29$, $P < .001$) and oxidized LDL ($r = -.19$, $P < .01$). Soluble VCAM-1 concentration was positively related to LDL cholesterol ($r = .38$, $P < .001$), triglycerides ($r = .16$, $P < .05$) and oxidized LDL ($r = .47$, $P < .001$), while a negative significant correlation was observed with HDL-c ($r = -.28$, $P < .001$). ICAM-1 was also inversely associated with HDL-c levels ($r = -0.21$, $P < .01$). Both VCAM-1 and ICAM-1 were negatively related to FMV ($r = -.24$ and $r = -.21$, respectively; both $P < .01$).

In a multivariate model, which took into account the effect of age, sex, diastolic blood pressure, body mass index, HDL-c, triglycerides, oxidized LDL, and brachial-artery diameter, we found that a low FMV was predicted by increasing age, oxidized LDL, and brachial artery diameter, while HDL-c was an independent predictor of a greater FMV. Serum levels of VCAM-1 and ICAM-1 were both predicted by lower HDL-c, while oxidized LDL were independent predictors of VCAM-1 concentration (Table 2).

Table 2. Multivariate Regression Analysis of FMV and Soluble Cell Adhesion Molecules in 184 Hyperlipemic Subjects

	β	P
FMV		
Age	−0.14	.05
Sex	0.06	NS
Diastolic blood pressure	−0.03	NS
Body mass index	0.00	NS
HDL-c	0.28	.001
Triglycerides	0.11	NS
Oxidized LDL	−0.21	.003
Brachial-artery diameter	−0.30	.001
VCAM-1		
Age	0.08	NS
Sex	−0.08	NS
Diastolic blood pressure	−0.07	NS
Body mass index	−0.08	NS
HDL-c	−0.37	.001
Triglycerides	−0.12	NS
Oxidized LDL	0.47	.001
ICAM-1		
Age	−0.004	NS
Sex	0.01	NS
Diastolic blood pressure	0.07	NS
Body mass index	−0.12	NS
HDL-c	−0.29	.002
Triglycerides	−0.15	NS
Oxidized LDL	0.11	NS

Abbreviations:FMV, flow-mediated vasodilation; HDL-c, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1.

DISCUSSION

The main findings of the present study are that (1) subjects with lower HDL-c values show increased levels of VCAM-1 and ICAM-1 and a parallel reduction in brachial-artery FMV; (2) the impairment in FMV is predicted by age, high oxidized LDL, and low HDL-c concentration; (3) VCAM-1 levels are predicted by low HDL-c and by oxidized LDL, while ICAM-1 only by low HDL-c; and (4) a significant inverse association was found between levels of soluble adhesion molecules and endothelial reactivity. Our results were obtained in a population of hyperlipemic patients without overt cardiovascular disease and with no concomitant cardiovascular risk factors and may not be extended to other populations.

At least 2 mechanisms are involved in the endothelial protection conferred by HDL. First, HDL determines a reduction in the LDL-mediated oxidative changes. Oxidized LDL play a key role in the impairment of endothelial reactivity as suggested in several studies.[5,11-13] Arterial vasodilation is mediated primarily by the endothelial release of nitric oxide,[17] the catabolism of which is enhanced by an increased oxidative state. Accordingly, the in vitro susceptibility of LDL to oxidation is related to an alteration in endothelium-dependent coronary vasodilation.[18] HDL antagonize the oxidative state through antioxidant enzymes and proteins, including platelet-activating factor, acetylhydrolase,[19] paraoxonase,[5,11-13] and apoprotein J,[20] all able to reduce the LDL oxidative potential. The polymorphisms of paraoxonase seem to influence coronary endothelial function in patients with clinical manifestations of coronary artery disease.[21] HDL is able to remove lysophosphatidylcholine from oxidized LDL, thus preventing the unfavorable effects of lysophosphatidylcholine on the endothelial cells,[22] and coincubation of HDL with endothelial cells prevents the displacement of nitric oxide synthase from caveolae induced by oxidized LDL.[23] In vivo, Toikka et al[5] showed that normocholesterolemic healthy subjects with low HDL-c exhibit higher values of oxidized LDL.

Circulating levels of oxidized LDL, which are known to have a positive correlation with LDL cholesterol, are a useful marker for cardiovascular risk stratification.[24,25] Also, in the present study, oxidized LDL showed a significant correlation with LDL cholesterol ($r = .49$, $P < .0001$) and was able to predict endothelial dysfunction and increased VCAM-1 levels.

The second mechanism involved in the endothelial protection conferred by HDL-c is its anti-inflammatory action. In this regard, the present report demonstrated that the concentration of soluble cellular adhesion molecules, namely VCAM-1 and ICAM-1, was predicted by low HDL-c values. HDL have an inhibitory effect on the expression of vascular cellular adhesion molecules[7,26] and on the expression of E-selectin induced by interleukin-1.[27] It is well known that proinflammatory cytokines induce the expression of adhesion molecules, which plays a critical role in the early phases of atherogenesis. A potential mechanism of HDL-mediated inhibition of adhesion molecule expression is the inhibition of sphingosine kinase, an enzyme involved in the modulation of endothelial adhesion molecule by tumor necrosis factor-α.[28] A few in vivo studies have suggested that soluble adhesion molecule levels are greater in hyperli-

pemia. In hypertriglyceridemic subjects, we observed an inverse relationship between the soluble forms of VCAM-1 and ICAM-1 and HDL-c.[9] Recently, Calabresi et al[10] described increased levels of ICAM-1 and E-selectin in both normolipemic and hypertriglyceridemic subjects with low HDL-c levels.

The oxidative state seems an important determinant of the chronic arterial inflammatory disease. In fact, the lysophosphatidylcholine component of oxidized LDL seems to be responsible not only for an inhibitory effect on endothelium-dependent vasodilation, but also for a selective increase in VCAM-1 and ICAM-1 expression in arterial endothelial cells.[29] In our study, only VCAM-1 levels were predicted by oxidized LDL (Table 2), while ICAM-1 was predicted by low HDL-c. It had been demonstrated previously that ICAM-1 expression on endothelial cells is mostly the consequence of proinflammatory stimuli.[30] No differences in E-selectin were observed between the groups at low and high HDL-c concentrations. Actually, E-selectin is expressed in the extremely initial phase of vessel damage, being the mediator of leukocyte rolling on endothelium.[31] The absence of E-selectin increase might indicate the presence of an initial vascular damage, as suggested by the evidence of endothelial dysfunction.

Some aspects of the present study deserve comment. First, in our study, the values of brachial FMV are rather low; endothelial reactivity, even in healthy subjects, is strictly dependent on the presence of cardiovascular risk factors,[32] as in our group of patients, hypercholesterolemia, increasing age (6th decade of life) and, in the low HDL-c group, the prevalence of male gender and hypertriglyceridemia. Second, we performed endothelium-independent vasodilation only in a small subgroup of patients because it is well known that lipid cardiovascular risk factors act through a nitric-oxide mechanism, which primarily affects endothelium-dependent vasodilation.[32]

We conclude that in hyperlipemic patients free of cardiovascular disease low HDL-c levels may affect endothelial dysfunction through a lack of oxidation inhibition and a concomitant overexpression of cell adhesion molecules.

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