Fluvastatin Improves Endothelial Dysfunction in Overweight Postmenopausal Women Through Small Dense Low-Density Lipoprotein Reduction

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Small dense low-density lipoprotein (sdLDL), which are often associated with obesity, are considered as the most atherogenic and have been shown to impair endothelial function. It is not known whether reduction of sdLDL by pharmacological intervention can improve endothelial function. Thirty-four consecutive postmenopausal women with ≥5.70 mmol/L total cholesterol were placed into either an overweight (body mass index [BMI] ≥ 25.0, n = 22) or a normal-weight (BMI < 25.0, n = 12) group, and forearm blood flow (FBF) was measured using strain-gauge plethysmography during reactive hyperemia before and after fluvastatin treatment. At baseline, the peak FBF during reactive hyperemia in the overweight group was less than that in the normal-weight group (mean ± SD, 13.6 ± 4.4 *v* 22.2 ± 4.0 mL/min/100 mL, *P* < .01). The maximal FBF after nitroglycerin was similar in both groups. In the stepwise multiple regression analysis, only the concentration of sdLDL was the predictor for peak FBF (standard coefficient = −0.517, *P* = .0115). The nonsignificant parameters for the correlations in the model were age, BMI, systolic blood pressure, the homeostasis model assessment of insulin resistance (HOMA-IR), hemoglobin A_{1c} (HbA_{1c}), and LDL-cholesterol. Fluvastatin treatment was associated with the recovery of the peak FBF in the overweight group but it did not influence that of the normal-weight group. Changes in sdLDL fractions by fluvastatin correlated well with the peak FBF recovery. These results suggested that an increased sdLDL was linked to endothelial dysfunction in overweight postmenopausal women and fluvastatin treatment improved endothelial dysfunction by decreasing the atherogenic sdLDL fraction in this population.

OBESITY IS associated with increased cardiovascular morbidity and mortality[1,2] and is now considered a major independent risk factor.[3] Endothelium-dependent vasodilatation is diminished in atherosclerotic coronary arteries and characterizes individuals who are at a high risk of developing atherosclerosis such as obese people.[4,5] Although increased low-density lipoprotein (LDL)-cholesterol concentrations have consistently been associated with endothelial dysfunction,[6] hypertriglyceridemia with low high-density lipoprotein cholesterol (HDL-C), which is often associated with obesity, has also been suggested to impair endothelium-dependent vasodilatation.[7] LDL comprises a heterogeneous group of particles, of which the small dense subfractions (sdLDL) are considered to be the most atherogenic.[8-10] sdLDL particles are often associated with the other components of obesity, elevated triglycerides, and low HDL-C,[11,12] but the atherogenic potential of sdLDL particles remains operative after adjustment for triglycerides or HDL.[13,14] Austin et al showed in a prospective study[15,16] that sdLDL particles strongly increases the risk of coronary heart disease (CHD).

Among the available lipid-lowering agents, fibrates[8] and niacin[17] were shown to alter the distribution of LDL subclasses. However, it has been controversial whether hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (HMGRIs) lower sdLDL.[18,19] März et al showed that fluvastatin produces a shift in LDL subfractions toward more large and buoyant, less atherogenic LDL particles, in postmenopausal women.[20] Recently, sdLDLs were shown to cause endothelial dysfunction independent of the plasma concentration of LDL-cholesterol, triglycerides, and HDL-C in healthy men.[21] Since sdLDL particles are known to be prevalent in overweight subjects,[11,12] we hypothesized that overweight postmenopausal women are the most vulnerable to endothelial injury through a rise in sdLDL. We therefore examined whether LDL subfractions were linked to endothelial dysfunction in overweight postmenopausal women, and, if so, whether fluvastatin could improve their endothelial function.

MATERIALS AND METHODS

Subjects

Thirty-four consecutive postmenopausal women with hypercholesterolemia (≥5.70 mmol/L) were placed into either an overweight (body mass index [BMI] ≥ 25.0, n = 22) or a normal-weight (BMI < 25.0, n = 12) group. Patients with a history of cardiovascular or cerebrovascular disease, hepatic or renal disease, tobacco abuse, or on hormone-replacement therapy were excluded. All participants were treated with fluvastatin 20 to 40 mg/d for 12 weeks to achieve total cholesterol less than 5.70 mmol/L. Before and 4 and 12 weeks after treatment, the forearm blood flow (FBF) was measured using strain-gauge plethysmography during reactive hyperemia. The study protocol complied with the Guidelines of the Ethical Committee of the University of the Ryukyus. Informed consent was obtained from all subjects.

Endothelial Function

FBF was measured using a mercury-filled silastic strain-gauge plethysmograph (EC-5R, D.E. Hokanson, Issaquah, WA) as previously described[22] with modifications.[5] The strain-gauge was attached to the right upper arm held above the right atrium and connected to a plethysmography device. A wrist cuff was inflated to 200 mm Hg to exclude the hand circulation from the measurements 1 minute before each measurement and throughout the measurement of FBF. The upper arm cuff was inflated to 40 mm Hg for 7 seconds in each 15-second cycle to occlude venous outflow from the arm using a rapid cuff inflator (EC-20, D.E. Hokanson). The FBF output signal was transmitted to a recorder (U-228, Advance Co, Nagoya, Japan). FBF was expressed as milliliters per minute per 100 mL of forearm tissue. Then the FBF was

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calculated by 2 independent observers who had no knowledge of the subjects' profile; the interobserver coefficient of variation was 3.0% ± 1.3%.

Study Protocol

The study began at 9 AM after the subjects fasted for at least 12 hours. The subjects were kept in the supine position in a quiet, dark, air-conditioned room (constant temperature 22°C to 25°C) throughout the study. After 30 minutes in the supine position, the basal FBF was measured. Then, the effect of reactive hyperemia and sublingual nitroglycerin on FBF was calculated. To induce reactive hyperemia, FBF was occluded by inflating the cuff on the right upper arm to a pressure of 200 mm Hg for 5 minutes. After release of the cuff, FBF was measured for 180 seconds. Nitroglycerin, 0.3 mg (Nihonkayaku Co, Tokyo, Japan) was then administered sublingually, and FBF was measured for 5 minutes. These studies were performed in a randomized fashion, and each study proceeded after FBF had returned to baseline. In the preliminary study, after the release of the cuff or the sublingual nitroglycerin, FBF returned to baseline within 10 minutes. Thus, the end of the response to reactive hyperemia or sublingual nitroglycerin was followed by a 15-minute recovery period. Baseline fasting serum concentrations of total cholesterol, HDL-C, triglycerides, insulin, and glucose were obtained after 30 minutes at rest.

Biochemical Measurements

Venous blood samples were obtained in tubes containing EDTA-sodium (1 mg/mL) and in polystyrene tubes without an anticoagulant. The EDTA-containing tubes were promptly chilled. Plasma was immediately separated by centrifugation at 3,000 rpm at 4°C for 10 minutes, and serum by centrifugation at 1,000 rpm at room temperature for 10 minutes. Samples were stored at −80°C until assayed. Routine chemical methods were used to determine the serum concentrations of total cholesterol, HDL-C, triglycerides, free fatty acids, creatinine, glucose, and electrolytes. The serum concentration of LDL was estimated using Friedewald's method.[24] LDL subfractions were determined using the Lipoprint LDL System (Quantimetrix, Redondo Beach, CA),[25] and malondialdehyde-modified LDL (MDA-LDL) by enzyme-linked immunosorbent assay.[26] Urinary 8-epi-prostaglandin-F2α (8-epi-PGF2α) was determined using a commercially available enzyme immunoassay kit (Assay Designs, Ann Arbor, MI) as described previously.[27]Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as described previously.[28]

Statistical Analysis

Values are expressed as the means ± SD. Two-tailed unpaired Student's *t* test was used to compare group means. Comparisons of time course curves of FBF during reactive hyperemia were analyzed by 2-way analysis of variance (ANOVA) for repeated measures on one factor followed by Bonferroni's correction for multiple-paired comparisons. The repeated factor was time of reactive hyperemia and the nonrepeated factor was one group versus the other group (Fig 1). Multigroup comparisons of variables, including maximal FBF response to nitroglycerin (Fig 2), were done by 1-way ANOVA followed by Bonferroni's correction. Probabilities were considered to be significant if less than .05. The data were processed using the StatView J-5.0 (SAS Institute, Cary, NC) software package.

RESULTS

Clinical Characteristics

Age and blood pressure were comparable between the normal-weight and overweight groups (Table 1). Body weight, BMI, and waist and hip circumferences were significantly higher in the overweight group than in the normal-weight group. The serum concentrations of glucose and insulin were higher in the overweight group. Urinary 8-Epi-PGF2α, a surrogate marker of oxidative stress, was slightly higher though not significant in the overweight group.

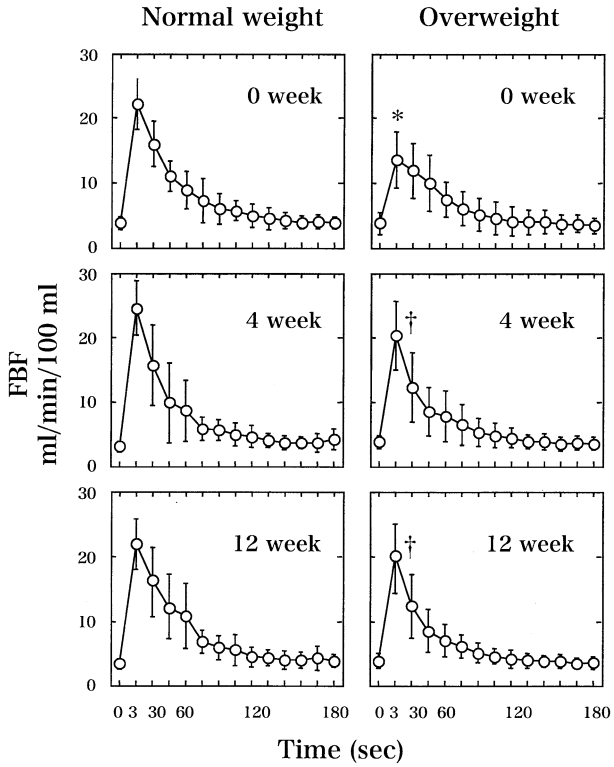

Fig 1. Effects of fluvastatin on FBF at rest and during reactive hyperemia in normal-weight (n = 12) and overweight (n = 22) postmenopausal women with mild hypercholesterolemia. FBF curves were obtained at 0, and 4 and 12 weeks after treatment with fluvastatin in both groups. Values represent the mean ± SD. The *P* value for the FBF curve difference between the normal-weight and overweight groups at 0 week was .0006 by 2-way ANOVA. Peak values were different at **P* < .001 from the normal-weight group and †*P* < .001 from 0 week.

Lipid Profiles and Endothelial Function

At baseline, the peak FBF during reactive hyperemia in overweight postmenopausal women was less than that in the normal-weight controls (13.6 ± 4.4 *v* 22.2 ± 4.0 mL/min/100 mL, $P < .01$) (Fig 1). The maximal FBF after sublingual administration of nitroglycerin was similar in the normal-weight and overweight groups (5.43 ± 0.64 *v* 4.93 ± 0.36 mL/min/100 mL, $P = .484$). The serum concentrations of total and LDL-cholesterol were comparable between the 2 groups, and the overweight group showed a trend toward a higher free fatty acid concentration ($P = .064$) (Table 2). There were no significant differences between the 2 groups regarding apolipoprotein variables. The overweight group showed a decrease of large buoyant LDL (lbLDL) fractions (LDL1 + LDL2) and an increase of sdLDL fractions (LDL3 to LDL7) as compared to the normal-weight group. Simple regression analysis indi-

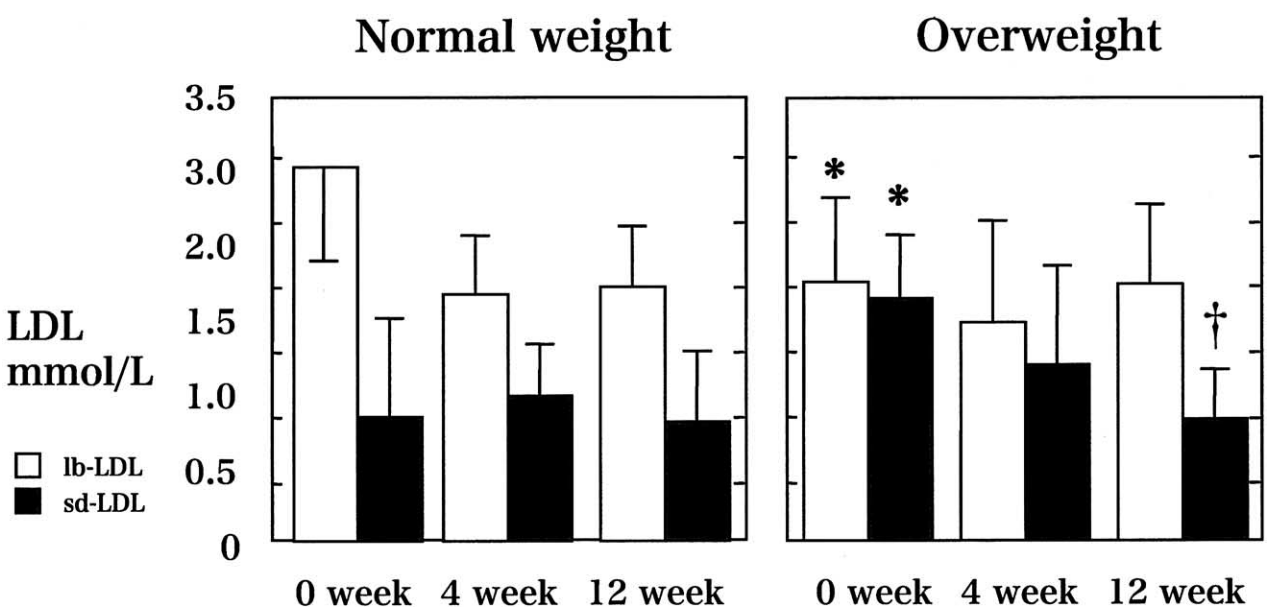

Fig 2. Effects of fluvastatin on plasma LDL-cholesterol subfractions in the normal-weight (n = 12) and overweight (n = 22) postmenopausal women with mild hypercholesterolemia. Large buoyant (□) or small dense (■) LDL concentrations were calculated as described in the Methods. Each column and bar represent the mean ± SD. *$P < .001$ different from the normal-weight group, and †$P < .001$ from 0 week.

cated that age, systolic and diastolic blood pressure, and fasting plasma glucose did not correlate with peak FBF (data not shown). On the contrary, the peak FBF significantly correlated with BMI and the serum concentrations of free fatty acids and MDA-cholesterol (Table 3). The peak FBF did not correlate with the concentrations of total cholesterol and total LDL, but it showed a good negative correlation with sdLDL fractions and a good positive correlation with lbLDL fractions (Table 3). Stepwise multiple regression analysis including both group patients showed that concentration of the sdLDL particles correlated with the peak FBF (standard coefficient = −0.517). The nonsignificant parameters for the correlations in the model were age (partial coefficient = 0.248), BMI (−0.352), systolic blood pressure (−0.064), HOMA-IR (−0.183), hemoglobin A_{1c} (HbA_{1c}) (0.074), and LDL-cholesterol (0.074). For the final regression model, the peak FBF = −0.517 × (sdLDL concentration) + 23.9 (adjusted $R^2 = 0.232$, $P = .0115$).

Table 1. General Characteristics of the Study Patients

	Normal Weight (n = 12)	Overweight (n = 22)
Age (yr)	63.0 ± 5.9	62.7 ± 6.7
Body weight (kg)	52.9 ± 5.5	63.6 ± 11.1*
BMI (kg/m^2)	23.3 ± 2.0	27.9 ± 3.7†
Waist circumference (cm)	89.1 ± 7.2	96.5 ± 11.1*
Hip circumference (cm)	91.4 ± 6.8	100.2 ± 10.5*
Waist/hip	0.98 ± 0.09	0.96 ± 0.07
Heart rate (beats/min)	67.8 ± 9.3	69.0 ± 7.1
Blood presssure (mm Hg)	132/73 ± 22/8	138/75 ± 23/13
Fasting glucose (mmol/L)	5.73 ± 2.73	6.31 ± 1.89
Fasting insulin (pmol/L)	45.1 ± 34.6	70.6 ± 34.7*
MDA-LDL (U/L)	131.0 ± 11.5	174.6 ± 11.6*
Urinary 8-iso-PG F2α (pg/mg creatinine)	235 ± 132	313 ± 137

NOTE. Values are mean ± SD.
*$P < 0.05$.
†$P < 0.01$ *v* normal weight.

Fluvastatin, sdLDL, and Endothelial Function

Fluvastatin treatment was associated with a recovery of the peak FBF in the overweight group but it did not influence the peak FBF of the normal-weight group (Fig 1). As shown in Table 2, fluvastatin decreased total cholesterol by 12.9%, LDL-cholesterol by 25.5%, and triglycerides by 5.6% in the normal-weight group, while in the overweight group, it decreased total cholesterol by 16.1%, LDL-cholesterol by 26.0%, and triglycerides by 25.4%. Treatment with fluvastatin decreased small dense LDL fractions only in the overweight group (Fig 2). Body weight, fasting plasma glucose, and HbA_{1c} were not different before and after floatation treatment in both groups (data not shown). Changes in sdLDL fractions by fluvastatin correlated well with the peak FBF recovery (Fig 3, lower panels). The improvement of the peak FBF induced by fluvastatin also correlated with a decrease in MDL-LDL ($R = -0.315$, $P = 0.0365$) and urinary 8-iso-PGF2α ($R = -0.310$, $P = .0425$).

DISCUSSION

The major findings of the present study were: (1) endothelial function was impaired in overweight postmenopausal women as compared to the normal-weight group; (2) the overweight group showed an atherogenic lipoprotein phenotype as indicated by a high level of sdLDL particles; (3) the concentrations of sdLDL fractions were closely associated with impaired endothelial function; and (4) fluvastatin reduced the concentra-

Table 2. Effects of Fluvastatin on Lipid Profiles

	Normal Weight (n = 12)			Overweight (n = 22)		
	0 Weeks	4 Weeks	12 Weeks	0 Weeks	4 Weeks	12 Weeks
Total cholesterol (mmol/L)	6.26 ± 0.58	5.45 ± 0.76	5.45 ± 0.59*	6.37 ± 0.68	5.30 ± 1.21*	5.34 ± 1.16*
Triglyceride (mmol/L)	1.57 ± 0.75	1.42 ± 0.54	1.48 ± 0.63	1.93 ± 0.81	1.71 ± 0.83	1.44 ± 0.62
HDL-C (mmol/L)	1.57 ± 0.38	1.69 ± 0.54	1.81 ± 0.52	1.51 ± 0.30	1.43 ± 0.43	1.50 ± 0.41
LDL-cholesterol (mmol/L)	3.95 ± 0.48	3.09 ± 0.61	2.94 ± 0.38*	3.95 ± 0.67	3.09 ± 0.78*	2.92 ± 0.82*
Free fatty acid (mmol/L)	0.62 ± 0.19	0.55 ± 0.13	0.68 ± 0.29	0.79 ± 0.28	0.55 ± 0.26*	0.60 ± 0.22*
Apolipoprotein A1 (g/L)	1.48 ± 0.28	1.52 ± 0.28	1.66 ± 0.27	1.50 ± 0.20	1.49 ± 0.40	1.52 ± 0.39
Apolipoprotein A2 (g/L)	0.29 ± 0.02	0.31 ± 0.04	0.31 ± 0.03	0.28 ± 0.04	0.28 ± 0.07	0.28 ± 0.07
Apolipoprotein B (g/L)	1.15 ± 0.10	0.99 ± 0.17	0.97 ± 0.13	1.21 ± 0.16	1.05 ± 0.27*	0.97 ± 0.23*
Apolipoprotein C2 (g/L)	0.05 ± 0.03	0.05 ± 0.01	0.06 ± 0.04	0.07 ± 0.05	0.05 ± 0.03	0.06 ± 0.03
Apolipoprotein C3 (g/L)	0.10 ± 0.02	0.11 ± 0.01	0.11 ± 0.02	0.11 ± 0.04	0.11 ± 0.05	0.10 ± 0.03
Apolipoprotein E (g/L)	0.05 ± 0.01	0.04 ± 0.00	0.05 ± 0.01	0.05 ± 0.01	0.05 ± 0.02	0.04 ± 0.01

NOTE. Values are mean ± SD.
*$P < .05$ *v* 0 weeks.

tions of sdLDL but not of lbLDL fractions and this reduction was associated with a concomitant improvement of endothelial function in the overweight group.

Endothelial Dysfunction

Endothelium-dependent vasodilation, which is mediated through the release of vasodilators such as nitric oxide (NO), has been reported to be inhibited in overweight people.[4] We examined the endothelial function of overweight and normal-weight postmenopausal women with hypercholesterolemia. The overweight group showed an impaired vasodilatation after reactive hyperemia as compared to the normal-weight group, while nitroglycerin-mediated vasodilatation was comparable. Steinberg and Baron reported that overweight subjects showed a blunted response of endothelium vasodilatation to methacholine, and that the response was not improved in euglycemic hyperinsulinemia.[4] They thus suggested that obesity was characterized by endothelial dysfunction mediated by endothelial resistance to insulin actions. In our study, fasting plasma glucose, insulin, HOMA-IR (a surrogate marker for insulin sensitivity),[28] and systolic blood pressure were higher in the overweight group, suggesting the contribution of multiple metabolic syndromes or insulin resistance.[6,7]

Table 3. Correlations Between Peak FBF and Biochemical Variables

	Peak FBF (mL/min/100 mL)		sdLDL (mmol/L)	
	*R**	*P*	*R**	*P*
Body weight (kg)	−0.336	.052	0.096	.532
BMI (kg/m^2)	−0.395	.020	0.163	.360
Waist circumference (cm)	−0.331	.056	0.057	.750
Waist/Hip	−0.039	.829	0.056	.756
Fasting glucose (mmol/L)	−0.292	.095	0.393	.021
Fasting insulin (pmol/L)	−0.322	.072	0.163	.375
HOMA-IR	−0.356	.058	0.397	.032
Total cholesterol (mmol/L)	−0.083	.645	0.302	.082
Triglyceride (mmol/L)	−0.325	.060	0.128	.474
HDL-C (mmol/L)	−0.002	.993	−0.087	.626
LDL-cholesterol (mmol/L)	0.117	.513	0.288	.099
Free fatty acid (mmol/L)	−0.421	.013	0.255	.146
Apolipoprotein B (g/L)	−0.103	.577	0.348	.050
MDA-LDL (U/L)	−0.402	.024	0.394	.028
lbLDL (mmol/L)	0.516	.002	−0.701	.000
sdLDL (mmol/L)	−0.436	.009	—	—
Urinary 8-iso-PG F2α (pg/mg creatinine)	−0.204	.321	.096	.643

**R:* Pearson's correlation coefficients for all subjects in the 2 groups (N = 34).

The Atherogenic Lipoprotein Phenotype

The overweight group showed an atherogenic lipoprotein phenotype, as evidenced by an increase in the concentration of sdLDL particles. It is well known that such atherogenic lipoprotein phenotype is associated with obesity.[11,12] The LDL subclass phenotype is known to be influenced by external factors, including drugs, menopausal status, and diet,[29] and it has also been suggested to be associated with insulin levels and insulin sensitivity.[30,31] In our study, sdLDL concentrations correlated with HOMA-IR. Since body weight and BMI did not correlate with sdLDL fractions, insulin resistance might have been mainly associated with such changes in LDL subfractions in overweight postmenopausal women. The atherogenic potential of small dense LDL is well recognized and has been ascribed to an increased susceptibility to oxidation,[8] lower binding affinity for the hepatic LDL apolipoprotein B/E receptor reflected in a prolonged presence in plasma,[9] and more efficient penetration of the arterial intima.[10] Thus, a reduction of the particle size of LDL appears to represent a key modification of this lipoprotein. Actually plasma MDA-LDL, a marker of oxidized LDL,[26] was increased in the overweight group, and also correlated with urinary 8-epi-PGF2α, a marker of oxidative stress,[27] in our study subjects ($R = 0.338$, $P = 0.046$). sdLDL and oxidative stress may be mutually linked to cause endothelial injury in overweight menopausal women.

sdLDL Fractions and Endothelial Function

Vakkilainen et al showed that the size of LDL was strongly associated with endothelial dysfunction, independent of LDL-cholesterol, triglycerides, and HDL-C in healthy men.[21] We showed that sdLDL fractions correlated negatively, while large LDL fractions correlated positively, with endothelial function

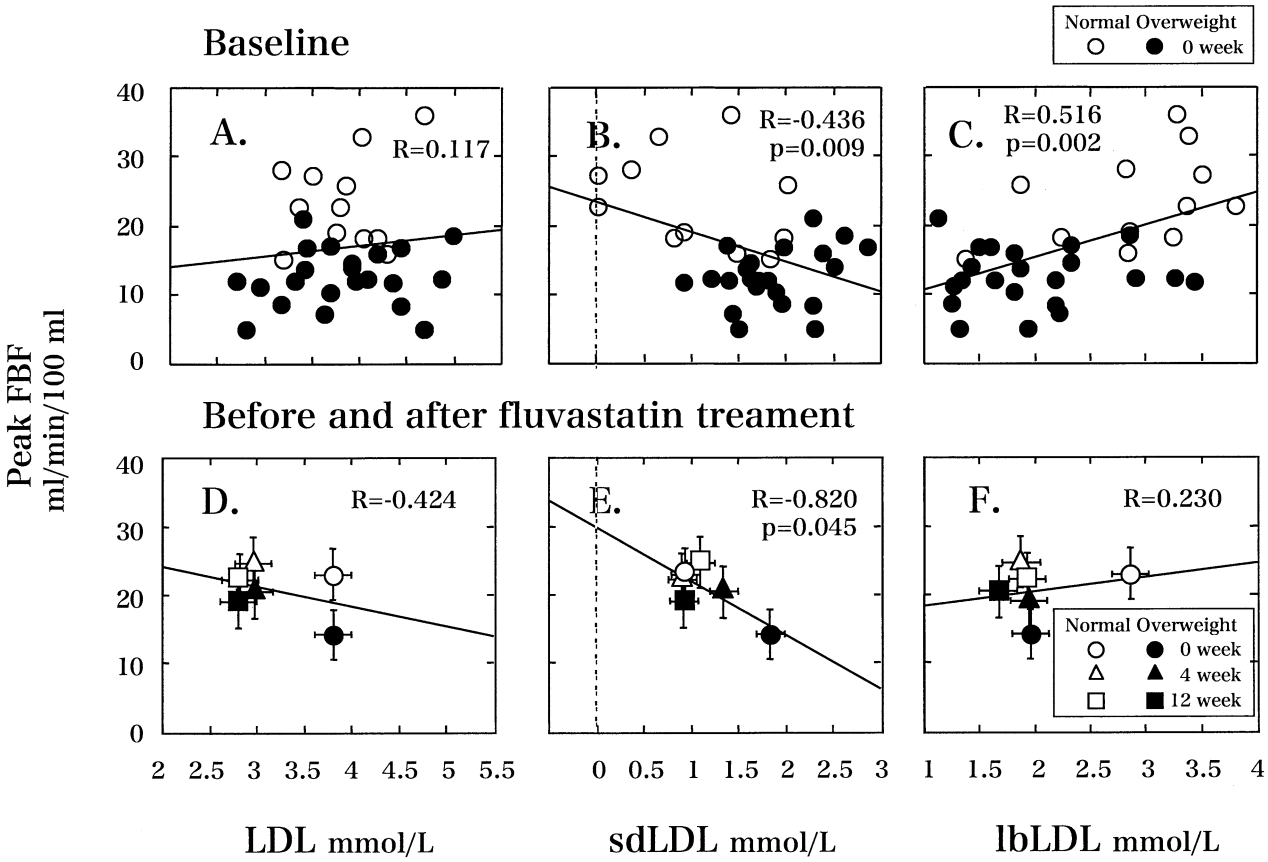

Fig 3. Correlations between the baseline peak FBF and (A) total cholesterol, (B) sdLDL, and (C) lbLDL in normal weight (n = 12, ○) and overweight (n = 22, ●) postmenopausal women with hypercholesterolemia. Correlations between peak FBF and (D) total cholesterol, (E) sdLDL, and (F) lbLDL concentrations at 0 (circles), 14 (triangles), and 12 (squares) weeks after treatment with fluvastatin in normal-weight (open) or overweight women (closed). Each value represents the mean ± SD. *R*: Pearson's correlation coefficients for all subjects of the 2 groups (N = 34).

in postmenopausal women. The difference in LDL subclass phenotype is not the result of menopause, but of obesity or insulin resistance. sdLDL is often associated with hypertriglyceridemia and low HDL-cholesterolemia, which are also common characteristics of obesity.[11,12] Although epidemiological studies have shown that hypertriglyceridemia is a significant determinant of cardiovascular events,[32] 2 reports have also shown that hypertriglyceridemia is not significantly associated with endothelial function.[33,34] In the current study, we observed that endothelial function and the concentration of serum free fatty acids, triglycerides, or the MDA-LDL content showed negative correlations. However, multivariate regression analysis showed that the concentration of LDL fractions was the most significant determinant of endothelial function. Thus the concentration of LDL fractions is an immediate determinant of endothelial function than serum triglycerides. After the first report that obesity was associated with endothelial dysfunction, Steinberg and Baron showed that an increase of free fatty acids derived from of exogenous or endogenous sources impaired endothelial function, suggesting that elevated free fatty acids levels were the crucial determinant of endothelial function in insulin-resistant overweight subjects.[4] We found that free fatty acids were another determinant of endothelial function. Since sdLDL did not correlate with the concentration of free fatty acids, sdLDL and free fatty acid may independently impair endothelial function.

Fluvastatin, sdLDL, and Endothelial Function

Although LDL subfractions was associated with endothelial function,[21] it remains unknown whether a change of LDL subfractions can modify endothelial function. In this study, we demonstrated that a decrease in sdLDL subfractions by pharmacological intervention was closely associated with an improvement of endothelial function. Fluvastatin improved endothelial function only in overweight women who are known to be at a greater risk for cardiovascular events due to sdLDL predominance.[12] Total and LDL-cholesterol and apolipoprotein B decreased by a comparable percentage in both groups, while sdLDL selectively decreased in overweight women. Fluvastatin on the distribution of LDL subfractions have been negative in normal-weight individuals.[18,19] However März et al[20] reported that fluvastatin effectively decreased sdLDL in postmenopausal women, who were at a greater risk for cardiovascular events.[12]

Thus it is possible that fluvastatin was selectively effective in our overweight subjects with the atherogenic lipoprotein profile. The mechanisms by which sdLDL subfractions were selectively decreased in overweight women were not clarified in the current study. We observed that changes in triglycerides and sdLDL did not correlate. Therefore, as previously suggested by März et al, alterations in VLDL metabolism (eg, reduced secretion of very-low-density lipoprotein or high lipoprotein lipase activity) cannot fully account for the changes in sdLDL induced by fluvastatin. Activation of hepatic lipase has been suggested to increase the formation of sdLDL by transferring triglycerides (interchangeable with cholesteryl esters) into LDL and HDL.[35] Since sdLDL subfraction and buoyant HDL-2b subfraction were inversely correlated, März et al suggested that hepatic lipase activity was decreased during fluvastatin therapy. They also reported that the activity of cholesteryl ester transfer protein was unchanged during fluvastatin therapy. Thus, they suggested that transfer of cholesteryl esters from HDL to apolipoprotein B–containing lipoproteins, which is another possible mechanism for sdLDL formation,[35] could not be involved.

The mechanisms linking the decrease of sdLDL particles to endothelial function in our study are not clear. It is well known that the small dense subfractions have a low-binding affinity to LDL receptors and are, at least partly via a prolonged residence time in plasma, easily oxidized. An enhanced susceptibility to oxidative modification could contribute to the greater atherogenicity of sdLDL.[8,33] In contrast with native LDL, oxidized LDL particles initiate a series of events, including vascular inflammation and macrophage foam cell formation, that are central to the atherogenic process.[36] LDL particles with a greater tendency to become oxidized might thus be more likely to participate in proatherogenic events. As an increased LDL permeability to endothelial cell monolayer can cause atherogenic process and this could be blocked by HMGRI,[37] interactions between LDL subfractions and endothelial barrier function by fluvastatin treatment need to be clarified. In our study populations, MDA-LDL, a marker for oxidized LDL,[26] correlated negatively with baseline endothelial function and the change induced by fluvastatin correlated with an improvement in endothelial function. Since the decrease in MDL-LDL was associated with the decrease in urinary 8-iso-PGF2α (R = 0.338, P = .046), fluvastatin might work as an antioxidant. This unique antioxidant characteristics of fluvastatin among other HMGRIs may at least partly explain the improvement of endothelial function observed in the present group of women.

In summary, endothelial function is impaired in overweight menopausal women with high concentrations of sdLDL fractions. Treatment with fluvastatin improved endothelial function by decreasing the concentrations of the atherogenic sdLDL fractions in this population at a high risk of cardiovascular events.

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