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Simvastatin Attenuates Plaque Inflammation

Evaluation by Fluorodeoxyglucose Positron Emission Tomography

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OBJECTIVES We investigated whether simvastatin attenuates plaque inflammation by using ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) co-registered with computerized tomography.

BACKGROUND Inflammation plays a key role in progression and destabilization of atherosclerotic plaque. ^{18}F-fluorodeoxyglucose PET is a promising tool for visualizing inflammation of atherosclerotic plaque. Antiinflammatory action is one of the pleiotropic effects of statins.

METHODS Forty-three consecutive subjects, who underwent ^{18}FDG-PET for cancer screening and had ^{18}FDG uptakes in the thoracic aorta and/or the carotid arteries, were randomized to either statin group receiving simvastatin (n = 21) or diet group receiving dietary management only (n = 22). The maximum standardized uptake values (SUVs) were measured in individual plaques, and were averaged for analysis of the subjectwise results. The responses were assessed after 3-month treatments.

RESULTS Positron emission tomography revealed 117 and 123 ^{18}FDG-positive plaques in the statin and diet groups, respectively. Simvastatin, but not diet alone, attenuated plaque ^{18}FDG uptakes and decreased the SUVs ($p < 0.01$). Simvastatin reduced low-density lipoprotein cholesterol (LDL-C) by 30% ($p < 0.01$) and increased high-density lipoprotein cholesterol (HDL-C) by 15% ($p < 0.01$), whereas LDL-C and HDL-C levels were not changed in the diet group. In the statin group, the decrease in the SUV was well correlated with the HDL-C elevation ($p < 0.01$) but not with the LDL-C reduction.

CONCLUSIONS ^{18}F-fluorodeoxyglucose PET visualized plaque inflammation and simvastatin attenuated it. The LDL-C–independent effects of simvastatin may participate in the beneficial effect. ^{18}F-fluorodeoxyglucose PET has a potential for visually monitoring plaque inflammation and the therapeutic effectiveness of statins. (J Am Coll Cardiol 2006;48:1825–31) © 2006 by the American College of Cardiology Foundation

Atherosclerosis is now widely accepted as a chronic vascular inflammatory disorder. Inflammation mediates various stages of atheroma development and progression from initial leukocyte recruitment to eventual rupture of the vulnerable plaque (1). Because of the singular properties of ^{18}F-fluorodeoxyglucose (^{18}FDG), a synthetic tracer that mimics the biochemical behavior of the natural glucose molecule, ^{18}FDG positron emission tomography (^{18}FDG-PET) has been established to be useful for detecting not only tumor cells but also inflammatory cells (2). Earlier retrospective studies reported that ^{18}FDG accumulation was incidentally detected in the aorta and the iliac and femoral arteries in 40% to 50% of patients who had undergone ^{18}FDG-PET for various clinical indications (3–5). Recently, Rudd et al. (6) have shown that ^{18}FDG accumulation corresponds to the macrophage-rich area of the plaque, which was endoatherectomized from ^{18}FDG-PET–positive carotid lesions. These observations suggested that ^{18}FDG-PET imaging is capable of visualizing atherosclerotic plaque inflammation.

Lipid-lowering therapy with statins significantly decreases cardiovascular morbidity and mortality in primary and secondary prevention (7,8). Statins exert their benefits through the inhibition of de novo cholesterol synthesis, resulting in significant reductions in plasma low-density lipoprotein cholesterol (LDL-C) levels. It remains controversial whether LDL-C lowering is the only mechanism for the observed beneficial effects. Many LDL-C–independent pleiotropic effects have been postulated. One of them is attenuation of inflammation because statins have been shown to decrease systemic inflammatory markers (9,10). However, no visual evidence that statins attenuate plaque inflammation has been documented noninvasively in clinical practice. ^{18}F-fluorodeoxyglucose PET may provide noninvasive longitudinal evaluation of plaque inflammation after statin therapy. Accordingly, in the present study, we investigated by serial ^{18}FDG-PET imaging whether simvastatin reduced inflammation of the plaques.

METHODS

Design and subjects. This study was a prospective, randomized, controlled study involving 3 months of study: drug administration and follow-up. The study protocol was approved by the Ethics Committee for the Clinical Research of Kurume University. All subjects gave written

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Abbreviations and Acronyms

^{18}FDG = ^{18}F-fluorodeoxyglucose
CT = computed tomography
HDL-C = high-density lipoprotein cholesterol
hsCRP = high-sensitivity C-reactive protein
LDL-C = low-density lipoprotein cholesterol
MRI = magnetic resonance imaging
PET = positron emission tomography

informed consent. The study included 43 consecutive subjects in whom ^{18}FDG-PET imaging for voluntary cancer screening revealed incidental ^{18}FDG uptakes in the thoracic aorta and/or the carotid arteries, including the innominate and the common carotid arteries and the extracranial segments of the internal and external carotid arteries. This study excluded subjects with active inflammatory diseases, dyslipidemia under medications, vasculitis, symptomatic coronary artery disease, symptomatic cerebrovascular diseases, and known systemic disorders such as hepatic, renal, hematologic, and malignant diseases.

Treatment. The study subjects were randomized to either diet group receiving dietary management (n = 22) or statin group receiving simvastatin in addition to dietary management (n = 21). Dietary management was performed according to the Japan Atherosclerosis Society Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases (11). In the statin group, the starting dose of simvastatin was 5 or 10 mg/day. When LDL-C level was more than 130 mg/dl (3.4 mmol/l) after 1 month of treatment, the dose of simvastatin was increased to 20 mg/day, the approved maximum dose in Japan. Consequently, the maintenance dose of simvastatin was 5 mg/day for 2 subjects, 10 mg/day for 14 subjects, and 20 mg/day for 5 subjects.

^{18}FDG −PET imaging. After at least 12 h of fasting, the study subjects received an intravenous administration of 4.2 MBq (0.11 mCi)/kg of ^{18}FDG. One hour after ^{18}FDG injection, 3-dimensional whole-body PET imaging was carried out using a PET scanner (Allegro, Philips Medical Systems [Cleveland], Inc., Cleveland, Ohio), which uses gadolinium oxyorthosilicate as the detector material. Contrast-enhanced computed tomographic (CT) images were also taken from the skull base to the diaphragm using Light Speed Ultra 16 (GE Healthcare, Milwaukee, Wisconsin). The co-registration of PET and CT images (software image fusion) was performed for review on a workstation (Sun Microsystems, Inc., Santa Clara, California) as described previously (6).

The ^{18}FDG-PET images were visually evaluated for the presence of abnormal ^{18}FDG uptakes in the aorta and the carotid arteries on the basis of the agreement of 3 radiologists specializing in nuclear medicine blinded to other clinical information and treatment assignments. Arterial uptake of ^{18}FDG was validated when co-registration of PET and CT showed that the accumulation overlapped on the vascular wall. The intensity of ^{18}FDG uptake was quantified by determining the standardized uptake value (SUV) corrected for lean body mass. A region of interest was placed on the transaxial image to totally surround the most intense area of the ^{18}FDG uptake, and the SUV was calculated by using the maximum pixel activity value within the region of interest. Special attention was given to match PET images of the same patient at baseline and at follow-up by measuring the distance from the carotid bifurcation for the carotid lesions or the distance from the top of the aortic arch for the aortic lesions, assessed by co-registered CT images. Two radiologists measured the SUV, and the measurements were averaged in each plaque. The intra- and interobserver variabilities of SUV measurements were <5%. If multiple abnormal areas of ^{18}FDG uptake were found in 1 vessel segment, and if they were each clearly distinguishable from one another, they were recorded separately. In individual plaques, the changes in the SUV (ΔSUV) were calculated by subtracting the SUV at baseline from the SUV after 3-month treatment. The subjectwise SUV and ΔSUV were calculated by averaging the plaquewise SUVs and ΔSUVs, respectively, in each subject.

Lipids and inflammatory markers. On the day of PET study, after overnight fasting, peripheral blood was drawn from the antecubital vein for the measurements of LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides,

Table 1. Baseline Demographics

	Diet Group (n = 22)	Statin Group (n = 21)
Age, yrs (range)	62 ± 6 (47–72)	65 ± 9 (45–77)
Male/female, n	14/8	13/8
Body mass index, kg/m^2	22.8 ± 2.0	23.6 ± 3.3
Systolic blood pressure, mm Hg	134 ± 14	130 ± 16
Pulse pressure, mm Hg	54 ± 10	54 ± 13
Plasma glucose, mg/dl	106 ± 14	102 ± 13
Hemoglobin A1c, %	5.5 ± 0.4	5.7 ± 0.8
CVD risk factor, n		
Current smoking	3	2
Former smoking	12	10
Hypertension	14	11
Hypercholesterolemia	10	9
Hypertriglycemia	9	8
Diabetes mellitus	3	4
History of cardiovascular diseases	2	3
Medications, n		
Aspirin	6	8
Antihypertensives	8	10
ARB or ACEI	5	7
Oral antidiabetics	2	2

Hypertension was defined by the presence of systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg or receiving antihypertensive medication. Hypercholesterolemia was diagnosed when low-density lipoprotein cholesterol was >130 mg/dl (3.4 mmol/l). Hypertriglyceridemia was defined when triglycerides were >150 mg/dl. Diabetes mellitus was defined by the presence of fasting plasma glucose >126 mg/dl and/or hemoglobin A1c >6.4% or receiving oral antidiabetics. "Antihypertensives" and "oral diabetics" denote the numbers of patients receiving any antihypertensive and antidiabetic agents, respectively.

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II type I receptor blockers.

glucose, hemoglobin A1c, and high-sensitivity C-reactive protein (hsCRP). They were measured at a commercial laboratory (SRL, Fukuoka, Japan).

Statistical analysis. Data are described as mean values ± SD. Paired and unpaired *t* tests were performed for comparisons between the baseline and follow-up and between the 2 groups, respectively. Pearson correlation coefficient was used for correlation analysis. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

Clinical characteristics. The baseline demographic profiles were well matched between the statin and the diet groups (Table 1). Their medications were not changed during the study. During the 3-month follow-up period, there were no significant changes in clinical characteristics except lipid profiles (Table 2). Although simvastatin tended to decrease hsCRP levels, the effect was inconsistent and did not reach the statistical significance.

^{18}FDG-PET imaging. As shown in Figure 1, abnormal focal ^{18}FDG uptakes were visualized in the transaxial images of the carotid arteries. Co-registration of PET and CT revealed that the ^{18}FDG uptakes were located eccentrically in the thickened arterial walls, suggesting that ^{18}FDG uptakes reflect atherosclerotic plaque inflammation. At baseline, a total of 117 and 123 inflammatory plaques were detected in the carotid arteries and the aorta of the statin and diet groups, respectively. The SUVs of the plaques at baseline did not differ between the statin and the diet groups.

After 3 months of treatment, simvastatin attenuated ^{18}FDG uptakes in the atherosclerotic plaques, whereas

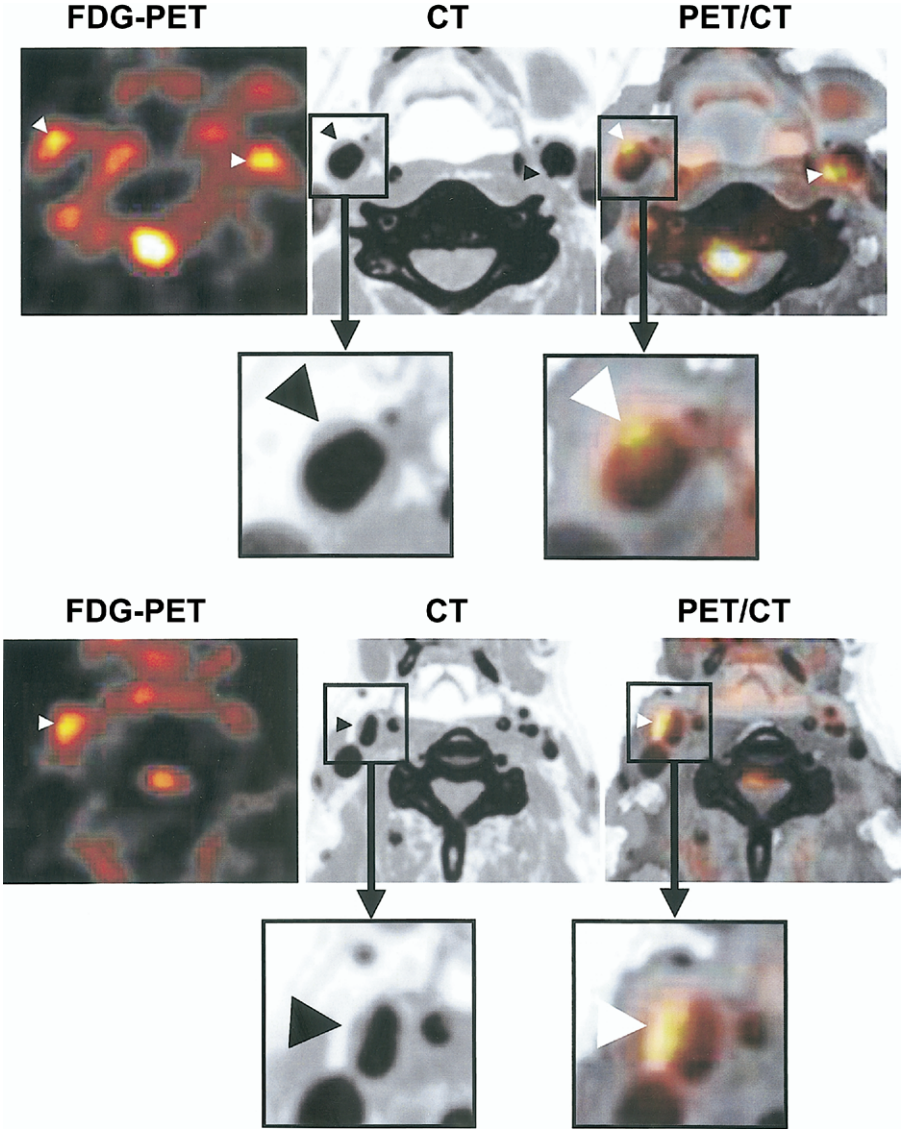

Figure 1. Representative transaxial images of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) **(left)**, enhanced computerized tomography (CT) **(middle)**, and co-registration of PET and CT (PET/CT) **(right)** showing ^{18}FDG uptakes in the carotid arterial plaques **(arrowheads)** of 2 patients.

Table 2. Changes in Clinical Characteristics and Plasma Lipids

	Diet Group (n = 22)		Statin Group (n = 21)	
	Baseline	Post-Treatment	Baseline	Post-Treatment
Body mass index, kg/m^2	22.8 ± 2.0	22.8 ± 2.2	23.6 ± 3.3	23.1 ± 2.6
Systolic blood pressure, mm Hg	134 ± 14	134 ± 17	130 ± 16	130 ± 15
Pulse pressure, mm Hg	54 ± 10	53 ± 13	54 ± 13	55 ± 14
Glucose, mg/dl	106 ± 14	107 ± 12	102 ± 13	106 ± 14
Hemoglobin A1c, %	5.5 ± 0.4	5.7 ± 0.5	5.7 ± 0.8	5.9 ± 1.1
LDL cholesterol, mg/dl	140 ± 27	142 ± 30	132 ± 27	93 ± 16*†
HDL cholesterol, mg/dl	55 ± 10	57 ± 11	51 ± 16	58 ± 13*
Triglycerides, mg/dl	141 ± 68	132 ± 67	156 ± 94	134 ± 75
hsCRP, mg/dl	0.09 ± 0.11	0.06 ± 0.07	0.11 ± 0.16	0.07 ± 0.06

Paired Student *t* test was performed for the comparison of the data before and after treatment for a given treatment group. Difference between 2 groups was examined using unpaired Student *t* test. *$p < 0.01$ versus baseline. †$p < 0.01$ versus diet group.
HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein.

dietary management alone did not (Fig. 2). Significant changes in the SUVs were observed only in the statin group ($p < 0.01$) (Fig. 3A). Also, the magnitude of the SUV change was significantly greater in the statin group than in the diet group ($p < 0.01$) (Fig. 3B).

Plasma lipids. At baseline, lipid profiles were similar between the statin and the control groups (Table 2). After 3 months of treatment, simvastatin reduced LDL-C by 30% ($p < 0.01$) and increased HDL-C by 15% ($p < 0.01$), whereas they were not changed in the diet group (Table 2, Fig. 4). In the statin group, the decrease in the SUV was well correlated with the increase in HDL-C level ($p < 0.01$), whereas there was no such correlation for LDL-C (Fig. 5). In the diet group, changes in the SUVs had no correlation with alterations in LDL-C or HDL-C.

DISCUSSION

Recently, ^{18}FDG-PET has emerged as a promising imaging modality for visualizing plaque inflammation. Our prospective, controlled, randomized trial has shown here for the first time by the use of ^{18}FDG-PET co-registered with enhanced CT that 3-month simvastatin treatment attenuates plaque inflammation. Although simvastatin decreased LDL-C and increased HDL-C, only the increase in HDL-C was correlated with the decrease in ^{18}FDG uptake. Thus, the antiinflammatory effect of simvastatin on atherosclerotic plaques may be one of the pleiotropic effects independent of LDL-C-lowering.

Noninvasive identification of inflammatory plaque has been challenging. With the recent advance in imaging technologies, we can get the morphology of plaques and some information about plaque stability (12,13) but cannot

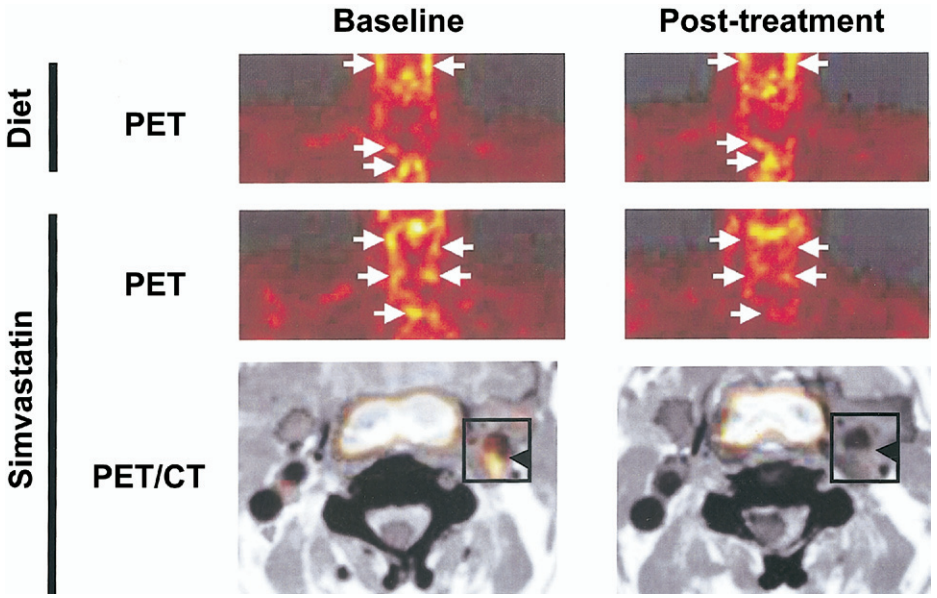

Figure 2. Effects of simvastatin on ^{18}FDG uptake in atherosclerotic plaque inflammation. Representative ^{18}FDG-PET images at baseline and after 3 months of treatment (post-treatment) with dietary management alone (diet) or simvastatin. **(Top)** Dietary management alone had no effect on ^{18}FDG uptakes **(arrows)** in the aortic arch and the carotid arteries. **(Middle)** ^{18}F-fluorodeoxyglucose uptakes were attenuated by simvastatin treatment. **(Bottom)** The co-registered images of ^{18}FDG-PET and CT clearly show that the plaque ^{18}FDG uptakes **(arrowheads)** disappeared after 3-month treatment with simvastatin. Abbreviations as in Figure 1.

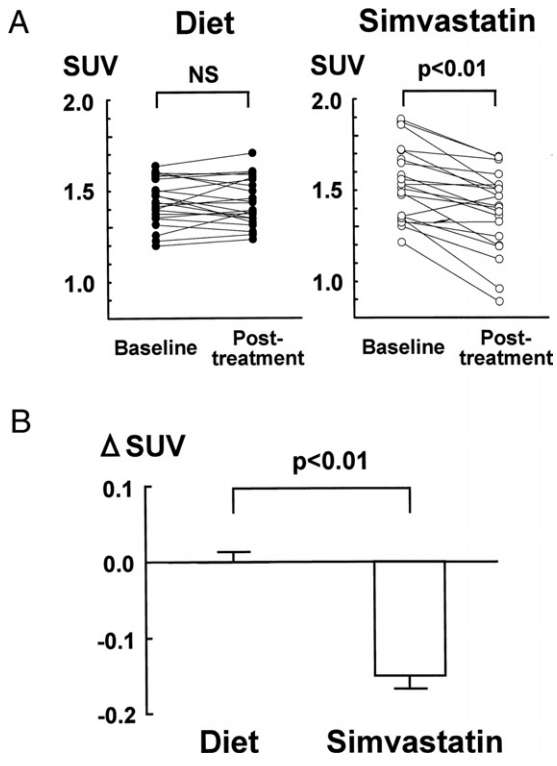

Figure 3. Quantitative analysis of the effects of simvastatin on ^{18}F-fluorodeoxyglucose uptake in atherosclerotic plaque inflammation. **(A)** For quantitative analysis, the maximum standardized uptake values (SUVs) were evaluated in individual plaques and averaged for analysis of the results of the subject-wise SUV at baseline and after 3-month treatment (post-treatment). **(B)** Changes in plaque SUVs from baseline. Plaque SUVs were significantly reduced by simvastatin, but not by dietary management alone (diet). ΔSUV denotes the changes in the SUV after treatment. Bar = 1 × SD.

see the inflammation directly. Because ^{18}FDG-PET can visualize tissue glucose metabolism with high sensitivity and we can quantify ^{18}FDG uptake in the region of interest, we used this metabolic imaging technique for the detection and monitoring of plaque inflammation. Although PET has limited spatial resolution, we showed that co-registration with CT can localize the ^{18}FDG uptake to individual atherosclerotic vessel walls (Fig. 1). This is consistent with previous studies showing that the co-registered ^{18}FDG-PET with CT (5,6) or high-resolution magnetic resonance imaging (MRI) (14) improved the accuracy of the diagnosis of plaque inflammation. The ^{18}FDG uptake has been attributed to infiltrating inflammatory cells (i.e., macrophages and lymphocytes) and subendothelial proliferation of macrophages and smooth muscle cells within atherosclerotic lesions (3,15–17). In an experimental rabbit model, ^{18}FDG accumulation corresponded to cellular infiltration in atherosclerotic lesions (18). Furthermore, it has been shown that ^{18}FDG is accumulated in the macrophage-rich area of the plaques, which were endoatherectomized from the PET-positive carotid lesions (6). These observations raised a possibility that serial ^{18}FDG-PET imaging is capable of surveying inflammatory activity within the plaque.

Blood pool activity may be a possible source of the vascular ^{18}FDG accumulation. However, it was unlikely in the present study. First, the co-registered image with CT clearly demonstrated that the uptakes were located in the vessel wall (Fig. 1). Second, vascular ^{18}FDG uptakes were not uniformly distributed along the course of the arteries (Fig. 2). In addition, nonvisualization of the large companion veins of the ^{18}FDG-labeled arteries was considered further indirect evidence against the blood pool hypothesis. Thus, it is unlikely that blood pooling activity is the major source of the vascular ^{18}FDG accumulation seen in the present study. Taken together, it is likely that the arterial ^{18}FDG uptakes are present in the vessel wall but not in blood pooling.

For quantitative analysis, we evaluated serial changes in the SUV within the plaque. The SUV is a quantified parameter of inflammation. So far, there has been no available information regarding the SUV levels of atherosclerotic plaques. In the present study, the plaque SUV at baseline was 1.69 ± 0.27 (ranging from 1.20 to 2.36) (Fig. 3A). The observed SUV levels were comparable to those seen in small gastric cancers or small metastatic thyroid tumors (19,20). Moreover, a very recent study has shown that given the SUV cut-off point of 1.30, ^{18}FDG-PET co-registered with enhanced CT has a sensitivity of 90.9% and a specificity of 88.8% for the diagnosis of active vessel inflammation in patients with aortitis syndrome (21). It was possible that high plasma glucose impaired FDG uptake in diabetic patients. Although 7 diabetic subjects were included in the present study, they were well controlled on dietary therapy with or without antidiabetics. In the statin and diet groups, there were no differences in the baseline SUV and the magnitude

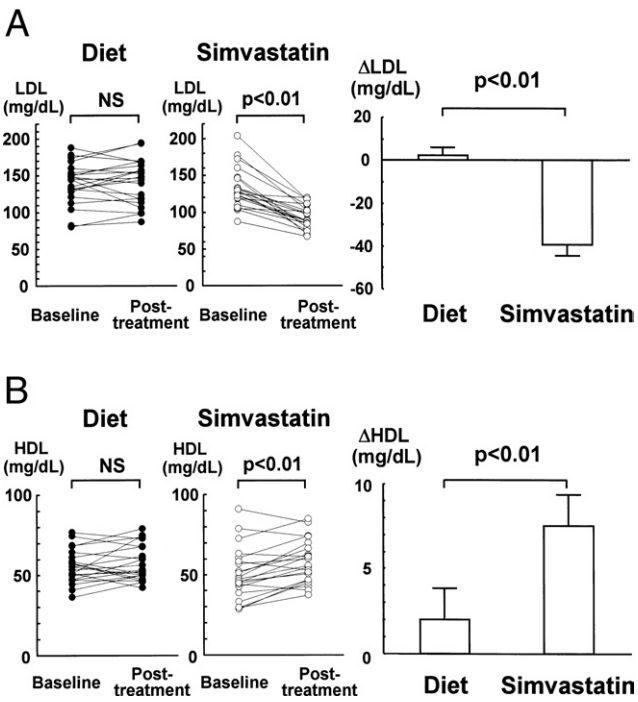

Figure 4. Changes in low-density lipoprotein (LDL) cholesterol **(A)** and high-density lipoprotein (HDL) cholesterol **(B)** after 3-month treatment with dietary management alone (diet) or simvastatin.

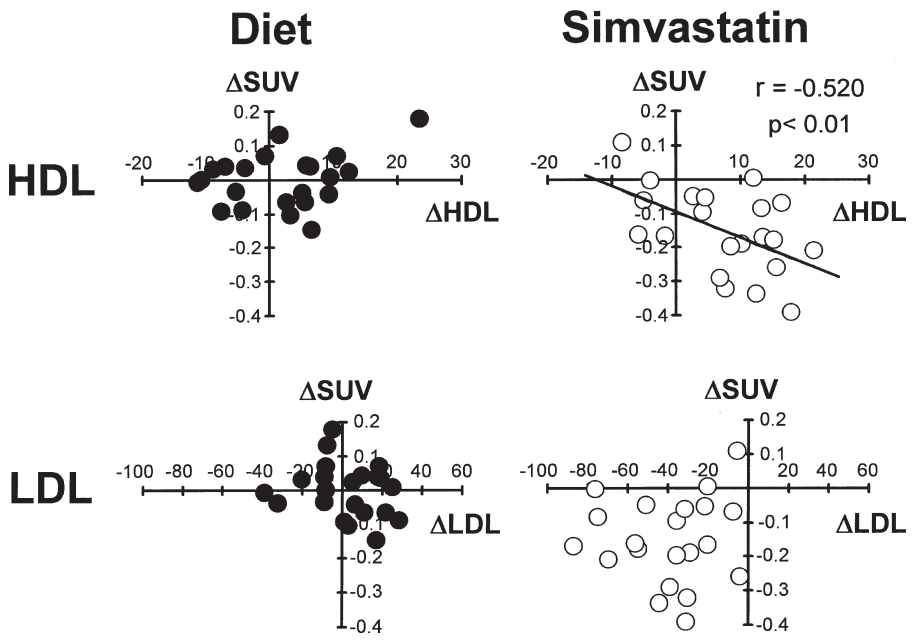

Figure 5. Correlations of changes in plaque ^{18}F-fluorodeoxyglucose uptakes (ΔSUV) with alterations in HDL cholesterol (ΔHDL, mg/dl) and LDL cholesterol (ΔLDL, mg/dl) after 3-month treatment with dietary management alone (diet) or simvastatin. ΔSUV had a significant correlation only with ΔHDL in the statin group. Abbreviations as in Figure 4.

of the SUV changes between diabetic and nondiabetic subjects (data not shown), suggesting that the presence of diabetes had no impact on the plaque FDG uptake in this study. Taken together, it is indicated that the observed ^{18}FDG uptake in the plaques indicates vessel inflammation. In our study, the intra- and interobserver variability was <5%, and repeated studies with the 3-month interval gave similar SUVs in the diet group. Thus, the SUV measurements had good reproducibility. Accordingly, the present study has indicated that atherosclerosis is an inflammatory process and that the individual plaque activities can be quantified by ^{18}FDG-PET in humans.

The most important finding of the present study is that ^{18}FDG-PET metabolic imaging can clearly visualize anti-inflammatory effects of simvastatin on the plaque (Fig. 2). Recent studies using high-resolution MRI demonstrated that it took more than 12 months for simvastatin to regress atherosclerotic plaques (12,13). Thus, although we did not examine the morphologic changes in this study, it is likely that in spite of the attenuation of plaque inflammation, the regression of the plaque might not have yet occurred in our patients with 3 months of simvastatin treatment. The observed anti-inflammatory effect of simvastatin may be related to the reduction of inflammatory cell infiltration and plaque stabilization. Crisby et al. (22) have demonstrated that patients after 3-month statin treatment had less lipid and oxidized LDL-C and fewer macrophages and T cells in the endatherectomized carotid samples compared with patients without statin. In the MIRACL (Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering) (23) and PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) (24) trials, significant benefits (i.e., the decreased incidence of unstable angina) occurred within the first month of treatment. Thus, our present study may support the hypothesis that the attenuation of plaque inflammation, rather than the anatomic regression, plays a role in the mechanism underlying the early beneficial effects of statins seen in clinical practice. In the present study, the effects of simvastatin on the serum CRP level, a systemic inflammatory marker, were not significant. One possible reason was the small size of the study. A second was the wide variability of the hsCRP levels in the present study. Another possibility is that the dose of simvastatin in this study (5 to 20 mg/day) was too small to reduce the systemic inflammatory marker. Future investigation with a larger study size is necessary to address this issue.

There were several possible mechanisms whereby simvastatin attenuated plaque inflammation. Simvastatin treatment reduced LDL-C by 30% (Table 2, Fig. 4). However, the reduction in the SUV was not correlated with the extent of LDL-C-lowering in the statin group (Fig. 5), suggesting that the LDL-C–dependent effect was the minor mechanism of the observed benefits. The reduction in plaque inflammation was correlated with the increase in HDL-C in the statin group. Thus, the HDL-C increase may be important in the mechanism of attenuation of plaque inflammation by simvastatin. However, it is also possible that pleiotropic effects other than HDL-C–dependent mechanism mediate the antiinflammatory effect of simvastatin on the plaque.

Study limitations. First, the small study size limits our interpretation and discussion. Second, longer drug administration and observation periods might provide us abundantly clear evidence of the anti-inflammatory effects of

simvastatin on the plaque. Third, the control group should have received lipid-lowering drugs (i.e., resins) to reduce the LDL-C to the same level of the statin group. However, the baseline LDL-C levels were not so high to warrant using other lipid-lowering drugs other than statins. Thus, we created the diet group as control. Next, several patients having aspirin and angiotensin II receptor blocker/angiotensin-converting enzyme inhibitor were included in the present study. We do not deny the possibility that anti-inflammatory properties of these agents may have enhanced the effects of simvastatin on the plaques. Finally, a future prospective study with a larger number of patients is needed to address whether the ^{18}FDG uptake is a predictor of cardiovascular events. Future technical innovations (e.g., the development of macrophage-specific PET tracers) would provide more specific information for detecting vulnerable plaques.

Conclusions. ^{18}F-fluorodeoxyglucose PET visualized inflammation of atherosclerotic plaques and that simvastatin attenuated it. The anti-inflammatory effect of simvastatin on the plaques may be one of the pleiotropic effects independent of LDL-C–lowering effects.

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