Reversal of Vascular ^{18}F-FDG Uptake with Plasma High-Density Lipoprotein Elevation by Atherogenic Risk Reduction

Su Jin Lee[1], Young Keun On[2], Eun Jeong Lee[1], Joon Young Choi[1], Byung-Tae Kim[1], and Kyung-Han Lee[1]

[1]*Department of Nuclear Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; and* [2]*Division of Cardiology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea*

Vascular ^{18}F-FDG uptake marker represents inflammation in atherosclerotic lesions, but whether inflammation can be reversed by risk-modifying interventions has not, to our knowledge, been demonstrated. In this study, we evaluated the change of vascular ^{18}F-FDG uptake in response to lifestyle intervention on serial PET/CT scans and further assessed how the findings relate to atherogenic risk reduction. **Methods:** A total of 60 healthy adults underwent ^{18}F-FDG PET/CT scans and atherogenic risk-factor assessment at baseline and again after 17.1 ± 8.3 mo of practicing lifestyle modification. The PET/CT images were evaluated for the presence of vascular ^{18}F-FDG lesions, and vessel–to–blood-pool ^{18}F-FDG ratios were measured. Indices from summed ratios of positive lesions were compared and correlated to atherogenic risk factors. **Results:** At follow-up, significant reductions in diastolic blood pressure ($P < 0.05$), total cholesterol ($P < 0.05$), and low-density lipoprotein level ($P < 0.05$) and an increase in high-density lipoprotein (HDL) level ($P < 0.0001$) were demonstrated. On the initial PET/CT scan, 50 of 60 subjects showed 1 or more ^{18}F-FDG–positive lesions (5.9 ± 5.0/subject), leading to a total of 352 vascular sites. On follow-up, ^{18}F-FDG–positive lesions were significantly reduced to 2.1 ± 2.2 sites per subject ($P < 0.0001$) and a total of 124 sites (64.8% reduction). Follow-up ^{18}F-FDG–positive rates were significantly reduced for the aorta and iliac arteries. In addition, significant reductions in the whole-body ^{18}F-FDG index from 1.39 ± 1.23 to 0.53 ± 0.59 ($P < 0.0001$) and carotid ^{18}F-FDG index from 0.08 ± 0.16 to 0.03 ± 0.06 ($P = 0.01$) were shown. The whole-body ^{18}F-FDG index correlated with total cholesterol ($P < 0.05$) and HDL level ($P < 0.05$), and the magnitude of reduction in the ^{18}F-FDG index closely correlated to the amount of increase in plasma HDL level ($P = 0.005$). **Conclusion:** Our study demonstrated that vascular ^{18}F-FDG uptake is reversed in response to atherogenic risk reduction by lifestyle intervention and that the magnitude of improvement correlates to increases in plasma HDL levels. Thus, serial ^{18}F-FDG PET/CT may be useful for monitoring improvements in the inflammatory component of atherosclerotic lesions in response to risk modification.

Key Words: atherosclerosis; ^{18}F-FDG PET; atherogenic risk factor; risk modification

J Nucl Med 2008; 49:1277–1282
DOI: 10.2967/jnumed.108.052233

Atherosclerosis is a leading cause of morbidity and mortality and a precursor to myocardial infarction and stroke (*1*). Over the years, lifestyle changes and lipid-lowering drugs have favorably influenced cardiovascular morbidity and mortality, and it has recently been established that such interventions can lead to a slowing and even regression of atherosclerosis (*2*,*3*). This result offers an impetus to identify preclinical atherosclerotic lesions to allow the application of appropriate strategies to prevent their progression and promote their regression (*4*). However, as the atherogenic process is contributed to by an overlap of multiple interacting processes, the direct effect of risk-modifying interventions on atherosclerotic lesions cannot be accurately assessed by conventional cardiovascular risk factors alone. Angiography is the present method of assessing the effect of risk factor modification but is invasive and inspects only limited regions of the vasculature. Furthermore, it cannot assess the cellular components and metabolic status of atherosclerotic lesions, which are more critical determinants of cardiovascular events than degree of luminal narrowing. Ultrasonography offers a simple method to assess the cumulative effect of atherosclerotic risk factors by measuring carotid intima–media thickness (IMT) but has limited penetrability for imaging of deep-seated arteries with sufficient spatial resolution or sensitivity (*5*).

PET with ^{18}F-FDG is a valuable diagnostic tool that is widely used to survey the whole body of patients for malignant and inflammatory disease (*6*), including inflammatory lesions of the vasculature (*7*). The cellular responses of atherosclerosis are also best described as an inflammatory disease (*8*), and correspondingly, ^{18}F-FDG uptake has been shown to be increased in arteries with active atherosclerosis (*9–11*). Furthermore, the presence of vessels with ^{18}F-FDG uptake has been associated with greater atherogenic risk

Received Feb. 27, 2008; revision accepted Apr. 25, 2008.
For correspondence or reprints contact: Kyung-Han Lee, Department of Nuclear Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Ilwondong, Kangnamgu, Seoul, Korea.
E-mail: khnm.lee@samsung.com

(*12,13*), and the cellular component that accumulates high levels of ^{18}F-FDG has been found to be infiltrating macrophages within the inflamed plaques (*14,15*). ^{18}F-FDG uptake of atherosclerotic lesions is a transient process that declines as the active inflammatory component recedes. If this were to occur in response to risk modification and were detectable by ^{18}F-FDG PET, it would provide an opportunity to noninvasively monitor the response of atherosclerotic lesions to intervention therapy (*4*). In this study, we investigated the change in ^{18}F-FDG uptake in major arteries on serial PET/CT scans of healthy adults that occurs in relation to atherogenic risk reduction induced by lifestyle modification.

MATERIALS AND METHODS

Study Subjects

The study subjects were 60 healthy adults who entered a regular health-screening program that included physical examination, blood pressure measurement, routine blood tests (including lipid profile, plasma glucose, and insulin), carotid sonography, and whole-body ^{18}F-FDG PET/CT. None of the subjects had malignancy, vasculitis, or any recent severe illness. Follow-up health screening including PET/CT scans was performed at an average of 17.1 ± 8.3 mo after the initial study, and no significant medical events during the interval were demonstrated.

Lifestyle modification was advocated for each subject at the end of the tests. Modification included individual dietary counseling by a registered dietitian and recommendations for physical exercise and weight reduction as indicated by a physician who informed the subjects of the test results.

^{18}F-FDG PET/CT

PET/CT was performed on a scanner (Discovery LS; GE Healthcare) after at least 6 h of fasting at 45 min after intravenous injection of 370 MBq of ^{18}F-FDG. Non–contrast-enhanced whole-body CT images were first acquired using an 8-slice helical CT scanner with a gantry rotation speed of 0.8 s. The following parameters were used to collect data: 80 mAs, 140 keV, a section width of 5 mm, and a table feed of 5 mm/rotation. PET emission images were then acquired from the thigh to the head for 5 min/frame. CT-based attenuation-corrected PET images were reconstructed using an ordered-subset expectation maximization algorithm (28 subsets, 2 iterations) and displayed in a 128 × 128 matrix (pixel size, 4.29 × 4.29 mm; slice thickness, 4.25 mm). Accurate coregistration of the CT and PET images was performed with commercially available software (Advantage Workstation; GE Healthcare).

Assessment of Vascular ^{18}F-FDG Uptake

^{18}F-FDG standardized uptake value (SUV) images were constructed with attenuation-corrected images, using injection dose, patient body weight, and a cross-calibration factor between the PET scanner and a dose calibrator. The images were visually evaluated for the presence of focal ^{18}F-FDG uptake on the vascular walls of the aorta (proximal, descending thoracic, and abdominal) and the common carotid, subclavian, and common iliac arteries on the basis of agreement between 2 nuclear physicians unaware of the results of the subject's laboratory tests. Lesions located from the aortic arch to the diaphragm were treated as multiple sites. Vascular peak SUV (pSUV) was measured from axial views of the ^{18}F-FDG PET images from regions of interest drawn over vessel walls as delineated by the CT images. All positive lesions, compared with blood-pool activity of the aortic arch, were confirmed to have ^{18}F-FDG pSUV ratios of greater than 1. ^{18}F-FDG–positive rates were defined as the proportion of subjects who had 1 or more positive lesions in a certain vascular region. The whole-body ^{18}F-FDG index was calculated as the sum of (vessel–to–blood-pool pSUV ratio − 1) of all ^{18}F-FDG–positive lesions in a subject. The carotid ^{18}F-FDG index was similarly calculated from all ^{18}F-FDG–positive carotid artery lesions.

Assessment of Atherogenic Risk Factors and Carotid Artery Ultrasonography

Atherogenic risk factors were assessed on the day of the PET/CT scan. Interviews provided subject age, sex, smoking habit, and presence of hypertension, diabetes mellitus, and statin medication. Physical examination evaluated systolic blood pressure (SBP), diastolic blood pressure (DBP), and body mass index (BMI). Laboratory tests included plasma levels of low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol, triglyceride, immune reactive insulin, fasting blood sugar (FBS), glycosylated hemoglobin A_{1c}, and high-sensitivity C-reactive protein (hsCRP).

Carotid artery IMT was measured in the posterior wall 10 mm proximal to the carotid bifurcation by high-resolution real-time B-mode ultrasonography (LOGIQ 7; GE Healthcare) in 29 and 52 subjects initially and at follow-up, respectively.

Statistical Analysis

All data are expressed as mean ± SD. The significance of differences in atherogenic risk factors between initial and follow-up studies was assessed by paired *t* tests with Bonferroni correction for multiple comparisons for continuous variables and χ^2 tests for rates of presence of risk and ^{18}F-FDG–positive vessels. Correlation between whole-body or carotid ^{18}F-FDG indices and atherogenic risk factors and the magnitudes of their changes were assessed by linear regression analysis. *P* values of less than 0.05 were considered statistically significant.

RESULTS

Initial Atherogenic Risk Factors at Initial and Follow-up Examinations

The clinical characteristics and atherogenic risk factors of the study subjects at initial and follow-up examinations are summarized in Table 1. The subjects were 55.9 ± 5.1 y old at the beginning of the study, and most were male (90%). On interview, 20 subjects (33%) reported the presence of hypertension, but elevated DBP (≥90 mm Hg) was disclosed in 8 and 5 subjects at initial and follow-up physical examinations, respectively. Similarly, whereas 5 patients (8%) were reported to have diabetes, 4 and 2 subjects showed high FBS levels (>110 mg/dL) at initial and follow-up blood tests, respectively. Statin was being used in 3 and 8 subjects at the time of initial and follow-up examinations, respectively.

Comparison of atherogenic risk factors revealed a significant reduction in DBP at follow-up, compared with initial levels. Furthermore, significant improvements throughout the lipid profile, including a significant increase in HDL levels and significant reductions in total cholesterol, LDL, and triglyceride levels at follow-up were found.

TABLE 1
Subject Characteristics and Atherogenic Risk Factors at Initial and Follow-up Studies

Data	Initial	Follow-up	*P*
Age (y)	55.9 ± 5.1	57.3 ± 4.9	—
Sex (male/female)	54/6	54/6	—
Current smoker	9	9	NS
Hypertensive (DBP ≥ 90 mm Hg)	20 (8)	20 (5)	NS
Diabetic (FBS > 110 mg/dL)	5 (4)	5 (2)	NS
Statin medication	3	8	0.06
BMI (kg/m^2)	24.1 ± 2.0	24.1 ± 1.9	NS
SBP (mm Hg)	120 ± 17	119 ± 16	NS
DBP (mm Hg)	78 ± 12	75 ± 12	0.04
Carotid IMT* (mm)	0.64 ± 0.15	0.72 ± 0.47	NS
Total cholesterol (mg/dL)	203 ± 36	193 ± 32	<0.01
LDL (mg/dL)	138 ± 28	129 ± 31	0.02
HDL (mg/dL)	52 ± 13	59 ± 13	<0.0001
Triglyceride (mg/dL)	135 ± 71	119 ± 54	0.03
FBS (mg/dL)	100 ± 19	96 ± 11	0.01
HbA1c (%)	5.5 ± 0.6	5.6 ± 0.6	NS
Immune reactive insulin (μIU/mL)	8.4 ± 3.6	9.1 ± 3.5	NS
hsCRP (mg/L)	0.09 ± 0.09	0.15 ± 0.30	NS

*n = 29 and 52 at initial and follow-up examinations, respectively.
HbA1c = glycosylated hemoglobin A_{1c}; NS = not significant.

^{18}F-FDG PET/CT Findings at Initial and Follow-up Examinations

On the initial PET/CT scan, 50 of 60 subjects (83.3%) showed 1 or more ^{18}F-FDG–positive lesions (average, 5.9 ± 5.0 lesions), leading to a total of 352 vascular sites. These were most frequent in the proximal aorta (n = 111, 31.5% of all lesions), followed by the abdominal (n = 100, 28.4%) and descending thoracic aorta (n = 88, 25.0%). The carotid, subclavian, and iliac arteries comprised 8.2%, 2.9%, and 4.0% of the lesions, respectively.

On the follow-up PET/CT scan, ^{18}F-FDG–positive lesions were significantly reduced to an average of 2.1 ± 2.2 sites per subject ($P < 0.0001$) and a total of 124 sites (64.8% reduction). Of these, 111 were new lesions, whereas only 13 were lesions from the initial PET/CT scan (reversal rate, 96.3%). The relative distribution of ^{18}F-FDG–positive sites was not different, with 37, 31, 39, 11, 5, and 1 lesions shown in the proximal, descending thoracic, and abdominal aortas and the carotid, subclavian, and iliac arteries, respectively. Figure 1 demonstrates an example in which an ^{18}F-FDG–positive lesion in the right common carotid artery found on the initial PET/CT scan had disappeared 1 y later on the follow-up PET/CT scan.

The ^{18}F-FDG–positive rate at follow-up was significantly reduced, compared with the initial study for the proximal (36.7% vs. 63.3%), descending thoracic (38.3% vs. 65.0%), and abdominal aortas (46.7% vs. 68.3%) and iliac arteries (0.8% vs. 10.8%) (Fig. 2). Semiquantitative analysis also demonstrated a significant reduction of the whole-body ^{18}F-FDG index from 1.39 ± 1.23 to 0.53 ± 0.59 ($P < 0.0001$) and carotid ^{18}F-FDG index from 0.08 ± 0.16 to 0.03 ± 0.06 ($P = 0.01$).

Relationship Between Arterial ^{18}F-FDG Uptake and Atherogenic Risk Factors

When ^{18}F-FDG indices pooled from all PET studies (initial and follow-up) were compared with atherogenic risk factors, a significant inverse correlation between the whole-body ^{18}F-FDG index and HDL (Fig. 3C) and a correlation between the carotid ^{18}F-FDG index and total cholesterol were demonstrated. Furthermore, the whole-body ^{18}F-FDG index showed significant correlations with total cholesterol at initial evaluation and with age, BMI, SBP and DBP, and hsCRP at follow-up (Table 2; Fig. 3). The magnitude of reduction in the whole-body ^{18}F-FDG index on follow-up

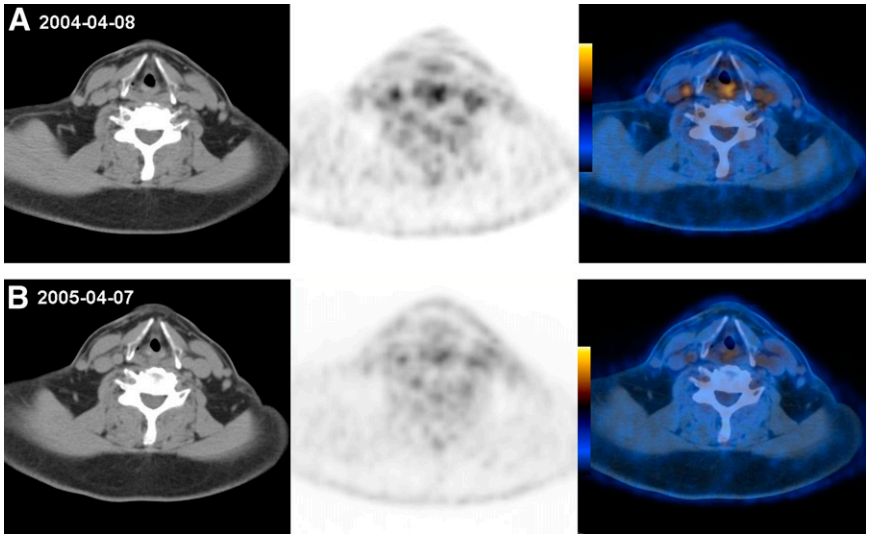

FIGURE 1. Serial ^{18}F-FDG PET/CT images of 62-y-old male patient. (A) Initial study demonstrates focal site of increased ^{18}F-FDG uptake in right common carotid artery. Lesion–to–blood-pool peak SUV ratio was 1.2. (B) On 1-y follow-up study, carotid artery lesion was no longer visible, and peak SUV ratio was reduced to 0.9.

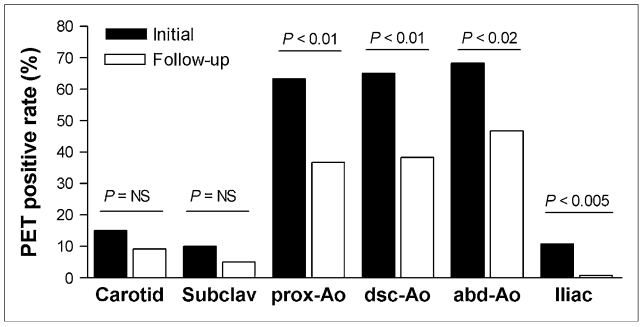

FIGURE 2. Comparison of PET-positive rates of major arteries on initial and follow-up studies. subclav = subclavian artery; proxAo = proximal aorta; dscAO = descending thoracic aorta; abdAO = abdominal aorta.

was found to significantly correlate to the amount of increase in plasma HDL levels (Fig. 3D; $P = 0.005$).

Although our study included 5 patients with diabetes mellitus, only 1 patient had significantly elevated blood glucose at the time of the ^{18}F-FDG injection and exclusion of this patient did not affect our study results. In addition, analysis excluding the 9 subjects who were treated with statin medication before or during the observation period still demonstrated an increase of HDL from 52.8 ± 13.7 to 59.2 ± 14.0 ($P = 0.02$); a significant correlation of whole-body ^{18}F-FDG index to DBP, BMI, and HDL; and a correlation between change in ^{18}F-FDG index and change in HDL level ($P = 0.003$).

We also evaluated the effect of excluding from analysis 21 subjects who showed no change in major atherogenic risk factors, because they could represent a subgroup with less successful lifestyle modification. After exclusion, the summed whole-body ^{18}F-FDG index still significantly decreased from 1.60 ± 1.34 at initial PET to 0.60 ± 0.75 at follow-up ($P < 0.00001$). In comparison, the respective values were 0.98 ± 1.07 and 0.41 ± 0.37 for the exclusion group. Also after exclusion, cholesterol and LDL were decreased and HDL increased at follow-up, and the follow-up whole-body ^{18}F-FDG index correlated with age and BMI and inversely correlated with HDL.

DISCUSSION

^{18}F-FDG PET is widely used in clinical diagnosis for its ability to detect ^{18}F-FDG accumulation in cells that have increased glucose metabolism. Recently, it has been established that ^{18}F-FDG PET can visualize atherosclerotic lesions by exploiting the high glycolytic activity of macrophages that infiltrate inflamed plaques. In this study, PET/CT was serially performed to investigate whether vascular ^{18}F-FDG uptake was reversed in response to lifestyle intervention and how this possible reversal related to atherogenic risk reduction. Because the study subjects were health-conscious, motivated individuals, they were expected to be highly compliant with the recommended lifestyle modifications; thus, significant improvements in major atherogenic risk factors were confirmed at follow-up. Coincidentally, ^{18}F-FDG uptake in most of the initially positive vessels was normalized on follow-up, whereas only a much smaller number of new lesions were found. Furthermore, the magnitude of reduction in ^{18}F-FDG uptake at follow-up correlated closely to the level of increase in plasma HDL.

On the initial PET/CT scan, our healthy subjects showed an 83.3% incidence of ^{18}F-FDG–positive arteries, a finding that is fairly consistent with previous observations made in patients undergoing cancer evaluation (*11,12*). As vascular ^{18}F-FDG uptake corresponds to atherosclerotic plaques with

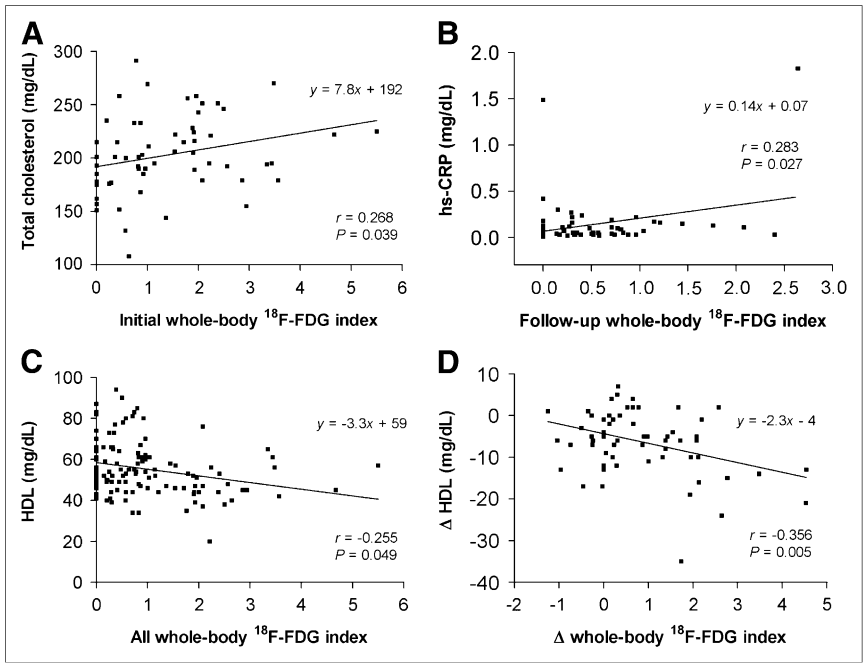

FIGURE 3. Linear regression results of whole-body ^{18}F-FDG index with atherogenic risk factors. Correlations are between index and total cholesterol at initial evaluation (A), between index and hsCRP level at follow-up (B), between index and HDL level at initial or follow-up evaluation (C), and between change in index and change in HDL level (ΔHDL) during observation period (D).

TABLE 2
Correlation Coefficient Values from Linear Regression Analysis of ^{18}F-FDG Uptake Indices and Atherogenic Risk Factors

Data	Whole-body ^{18}F-FDG index			Carotid ^{18}F-FDG index		
	Pooled	Initial	Follow-up	Pooled	Initial	Follow-up
Age	0.138	0.181	0.328*	0.181	−0.044	0.234
BMI	0.161	−0.005	0.562†	−0.005	0.077	0.165
Carotid IMT	−0.171	−0.463	−0.121	−0.463	0.172	0.002
SBP	0.115	0.038	0.282*	0.038	0.186	0.016
DBP	0.156	0.071	0.257*	0.071	0.106	0.176
Total cholesterol	0.141	0.268*	−0.320	0.268*	−0.072	−0.328
LDL	0.099	0.204	−0.247	0.204	−0.088	−0.209
HDL	−0.255*	−0.179	−0.220	−0.179	0.004	−0.198
Triglyceride	0.016	−0.039	−0.040	−0.039	−0.090	−0.135
FBS	0.016	−0.012	−0.126	−0.012	−0.075	−0.122
hsCRP	0.101	0.195	0.279*	0.195	0.157	−0.077

*$P < 0.05$.
†$P < 0.0001$.
Pooled data were obtained from both initial and follow-up PET/CT studies.

inflammatory macrophages and normal vessels do not show measurable uptake on PET (*14,15*), our findings appear to illustrate the high prevalence of clinically silent atherosclerotic vessels in otherwise healthy adults (*16*). In our study, the magnitude of vascular ^{18}F-FDG uptake was shown to correlate with atherosclerotic risk factors including low HDL, high LDL, high total cholesterol levels, and high systemic blood pressure. Similar relationships have been observed between large-vessel ^{18}F-FDG uptake and the male sex (*10*), older age (*12*), hypertension (*10,13*), hyperlipidemia (*9,12*), low HDL (*13*), and elevated hsCRP (*13*).

Although most previous studies of vascular ^{18}F-FDG have been performed on patients with cancer, we made this observation in otherwise healthy subjects, because direct metabolic effects from malignancy or from anticancer therapy may confound the results. Another unique feature of our study is that the pattern of vascular ^{18}F-FDG uptake was serially monitored over 1 or 2 y as subjects underwent lifestyle modifications aimed at reducing their cardiovascular risk. It has been shown that vascular ^{18}F-FDG uptake measurements are highly reproducible when PET is repeated at 2 wk (*17*). However, attempts to evaluate interscan reproducibility after significantly longer durations confront the difficulty of discerning observer variability from true vascular changes. We therefore looked at the subset of 21 study subjects who showed no change in major atherogenic risk factors during the observation period. As a result, the difference in the summed whole-body ^{18}F-FDG index between the 2 PET studies tended to change less between studies when atherogenic risk remained constant. Furthermore, in subjects without a change of risk factors, a significant correlation in vascular region ^{18}F-FDG index on initial and follow-up PET studies (Spearman $r = 0.41$, $P < 0.0001$) was seen. These findings indicate that the changes in ^{18}F-FDG uptake measured in our study more likely reflect divergent vascular states associated with atherosclerosis rather than interscan observer variability. However, we cannot completely exclude the possibility that interscan observer variability contributed to at least part of the changes in ^{18}F-FDG uptake measured in our study.

Much of the protective effect of risk-modifying interventions is mediated through improved blood pressure and lipoprotein levels, particularly by increasing HDL levels (*18*), and such improvements were indeed seen in our subjects. At follow-up, 96.3% of the initially positive vessels showed reversal of ^{18}F-FDG uptake, whereas substantially fewer new sites appeared, and semiquantified ^{18}F-FDG indices also significantly decreased. The magnitude of vascular ^{18}F-FDG uptake measured by PET appears to mirror the inflammatory activity and macrophage content of the lesions (*19*). Although virtually all atherosclerotic lesions contain at least some macrophages, ^{18}F-FDG uptake is likely no longer visible on PET when the number of infiltrating macrophages falls below a certain sensitivity threshold.

We observed that the magnitude of reduction in ^{18}F-FDG uptake on follow-up PET/CT correlated closely with the amount of increase in HDL during the same period. This finding relates to a recent report by Tahara et al. in which carotid artery ^{18}F-FDG uptake levels decreased with simvastatin treatment with an accompanying increase in plasma HDL (*20*). It is established that HDL levels inversely correlate to cardiovascular risk in humans, which has been attributed to the antiatherogenic properties of HDL that mediate reverse cholesterol transport from peripheral tissues and macrophages to the liver for excretion (*21*).

CONCLUSION

The results of this study demonstrate that vascular ^{18}F-FDG uptake that correlates with atherogenic risk factors is significantly reversed with risk reduction through lifestyle

modification, and the magnitude of reversal closely correlates with the amount of increase in plasma HDL. Therefore, serial ^{18}F-FDG PET/CT may have a role as a noninvasive method to monitor the response of inflammatory change in atherosclerotic lesions to risk modification therapy.

ACKNOWLEDGMENTS

This work was supported by Samsung grant C-A6-419-2, Korea. This work was presented in part at the 53rd annual meeting of the Society of Nuclear Medicine, San Diego, California, June 3–7, 2006.

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