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Decreased ^{18}F-Fluorodeoxyglucose Uptake in Lumbar Vertebrae of Stroke Patients

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Background and Purpose We investigated ^{18}F-fluorodeoxyglucose (FDG) uptake levels in the lumbar vertebrae, liver, and spleen of stroke patients with carotid atherosclerosis.

Methods This study analyzed acute ischemic stroke patients with carotid atherosclerosis who underwent whole-body FDG positron-emission tomography between October 2015 and January 2017. FDG uptake in the lumbar vertebrae, liver, and spleen was measured and compared between stroke patients and control subjects without stroke history. Multivariate linear regression analysis was performed to identify independent factors related to FDG uptake in the proximal internal carotid artery (ICA).

Results Twenty stroke patients aged 75.1±9.0 years (mean±standard deviation; 10 females) and 20 control subjects aged 62.9±10.7 years (6 females) were included. In comparison with the control group, the stroke group showed significantly higher FDG uptake in the proximal ICA (1.16±0.26 vs. 0.87±0.19, p<0.01), but significantly lower FDG uptake in the lumbar vertebrae (1.09±0.26 vs. 1.38±0.38, p=0.007) and liver (1.71±0.30 vs. 2.01±0.34, p=0.005). Multivariate linear regression analysis showed that the lumbar FDG uptake was negatively correlated with FDG uptake in the proximal ICA (standardized coefficient=-0.367, p=0.013) after adjusting for age and hypertension.

Conclusions Stroke patients showed decreased FDG uptake in the lumbar vertebrae. Further studies are warranted to evaluate the pathophysiological link between cerebral atherosclerosis and bone.

Key Words cerebral atherosclerosis, bone, positron-emission tomography.

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INTRODUCTION

Atherosclerosis progression and plaque rupture involves multiple pathological steps, including dysregulated progenitor cell production from hematopoietic organs, inflammatory cell recruitment, and phenotype alteration within an atheroma.[1,2] Several studies have recently applied ^{18}F-fluorodeoxyglucose (FDG) positron-emission tomography (PET) to investigate the relationship between hematopoietic organ activity and atherosclerosis in patients with coronary artery disease.[3,4] Observational studies have found that increased FDG uptake in the lumbar vertebrae and spleen is associated with elevated serum high-sensitivity C-reactive protein (hsCRP) and increased vascular events.[4] The FDG uptake of these hematopoietic organs is also reportedly elevated in patients with stable coronary artery disease, which reflects the involvement of excessive inflammatory progenitor cell production in the progression of coronary atherosclerosis.[5] However, the FDG uptake pattern in hematopoietic organs and its relation with inflammation have not been investigated in stroke patients.

We investigated FDG uptake in solid organs including the lumbar vertebrae, spleen, and

liver in stroke patients who had been included in a prospective study comparing FDG and ^{18}F-sodium fluoride (NaF) uptake in the proximal internal carotid artery (ICA) for detecting symptomatic atherosclerosis.

METHODS

Patient inclusion

The stroke cohort included the patients from a previous study that examined the diagnostic value of FDG and NaF ligands in detecting symptomatic carotid atherosclerosis in acute cerebral infarction patients.[6] Acute ischemic stroke patients admitted to Chung-Ang University Hospital with more than 50% carotid stenosis measured by computed tomography (CT) angiography were eligible. The control cohort consisted of apparently healthy subjects without previous stroke or active cancer who had undergone brain CT angiography and whole-body FDG PET in a health promotion center.[7] We excluded patients with active cancer or autoimmune disorder, advanced renal impairment (estimated glomerular filtration rate of <30 mg/mmol), uncontrolled diabetes, or other unstable medical conditions. We reviewed and compared clinical and laboratory variables from the two cohorts.

The study protocol conforms to the ethical guideline of the 1975 Declaration of Helsinki. This study was reviewed and approved by the Institution Review Board of Chung-Ang University Hospital (C2015061), and written informed consent was obtained from each patient included in the study.

PET evaluation

Whole-body PET and CT was performed with a combined scanner (Gemini TF 16, Philips Medical Systems, Cleveland, OH, USA) using the same protocol for the two cohorts. In brief, 259–370 MBq (7–10 mCi) of FDG was injected intravenously after 8 hours of fasting. Approximately 60 min after the injection, PET images were acquired for 5 min/bed for the head and 1 min/bed from the skull base to the proximal thigh, immediately after performing CT scanning (120 kVp, 50 mA). The median time from stroke onset to PET was 17 days (range=3–37 days) in the stroke patients, because PET was not performed until a patient was neurologically stabilized. The mean standardized uptake values (SUVs) of the liver, spleen, and fourth lumbar vertebra were determined as described previously.[7] The maximum target-to-background ratio (TBR) of the proximal ICA was derived by dividing the SUV of the proximal ICA by the SUV of the ascending aorta.

Statistical analysis

Categorical and dichotomous variables were expressed as the number and percentage of patients and compared using the chi-square test. Continuous variables were expressed as mean±standard-deviation values and compared using Student's *t*-test. Clinical and laboratory variables were compared between stroke patients and control subjects. FDG uptake in the ICA was compared using the maximum TBR, and FDG uptake in the solid organs was compared using the mean SUV. The correlations between FDG uptake in the solid organs and laboratory variables were analyzed to identify the mechanistic link of FDG uptake in the vertebrae, liver, and spleen after merging the two cohorts.

Since FDG uptake in a carotid atheroma is known to reflect its vulnerability,[8] multivariate linear regression analysis was performed to identify factors that were independently associated with FDG TBR in the ICA by including significant variables from bivariate analysis. We also performed another multivariate linear regression analysis with vertebral FDG level as a dependent variable.

All statistical analyses were performed using SPSS software (version 22.0, IBM Corp., Armonk, NY, USA), and $p<0.05$ was regarded as statistically significant.

Table 1. Demographic and clinical variables of the stroke patients and control subjects

	Control	Stroke	*p*
Number of subjects	20	20	
Age, years	62.9±10.7	75.1±9.0	0.001
Female	6 (30)	10 (50)	0.197
BMI, kg/m^2	24.1±3.9	22.9±3.8	0.299
Hypertension	7 (35)	17 (85)	0.001
Diabetes mellitus	5 (25)	13 (65)	0.011
WBC, ×10^9/L	6.7±2.1	7.3±1.6	0.397
Hematocrit, %	41.1±5.6	39.7±7.0	0.510
Platelet count, ×10^9/L	238±62	233±79	0.809
Neutrophils, %	61.9±9.5	61.3±10.0	0.830
FBG, mg/dL	106±18	161±70	0.002
Total cholesterol, mg/dL	195±51	178±58	0.327
hsCRP, mg/dL	7.10±20.10	4.15±5.70	0.531
Proximal ICA maximum TBR	0.87±0.19	1.16±0.26	<0.001
Liver SUV	2.01±0.34	1.71±0.30	0.005
Spleen SUV	1.68±0.34	1.53±0.31	0.174
L4 SUV	1.38±0.38	1.09±0.26	0.007
L5 SUV	1.33±0.36	1.10±0.32	0.033

Data are mean±standard-deviation or *n* (%) values.
BMI: body mass index, FBG: fasting blood glucose, hsCRP: high-sensitivity C-reactive protein, ICA: internal carotid artery, L4: fourth lumbar vertebra, L5: fifth lumbar vertebra, SUV: standardized uptake value, TBR: target-to-background ratio, WBC: white blood cell count.

RESULTS

The stroke cohort consisted of 20 stroke patients (age=75.1±9.0 years, including 10 females), and another 20 control subjects were recruited from a health promotion center for the control cohort (age=62.9±10.7 years, including 6 females). Comparing the basic demographic and vascular-risk-factor profiles revealed that the stroke population was significantly older and had a higher prevalence of hypertension and diabetes mellitus (Table 1). Representative images and quantitative analysis showed that FDG uptake in the lumbar vertebral bodies was significantly lower while that in the proximal ICA was significantly higher in stroke patients (Table 1 and Fig. 1A, B, and C). The splenic FDG uptake did not differ significantly between the two groups (Table 1). The FDG uptake in the lumbar vertebrae was negatively correlated with FDG uptake in the proximal ICA (Pearson's correlation coefficient= -0.491, p=0.001) (Fig. 1D).

Analysis of the correlations between solid-organ FDG uptakes and laboratory data revealed that FDG uptake in the lumbar vertebrae was positively correlated with the white blood cell count (WBC), hematocrit, and serum alkaline phosphatase (ALP) levels, and negatively correlated with age (Table 2). FDG uptake in the liver was significantly correlated with body mass index (BMI), hematocrit, serum ALP, and FDG uptakes in the lumbar vertebrae and spleen (Table 2). FDG uptake in the spleen was significant correlated with BMI but not with hsCRP (Table 2).

Bivariate linear regression analysis showed positive correlations of the age, history of hypertension, and presence of stroke with the proximal ICA FDG uptake (Table 3). The proximal ICA FDG uptake was significantly negatively corre-

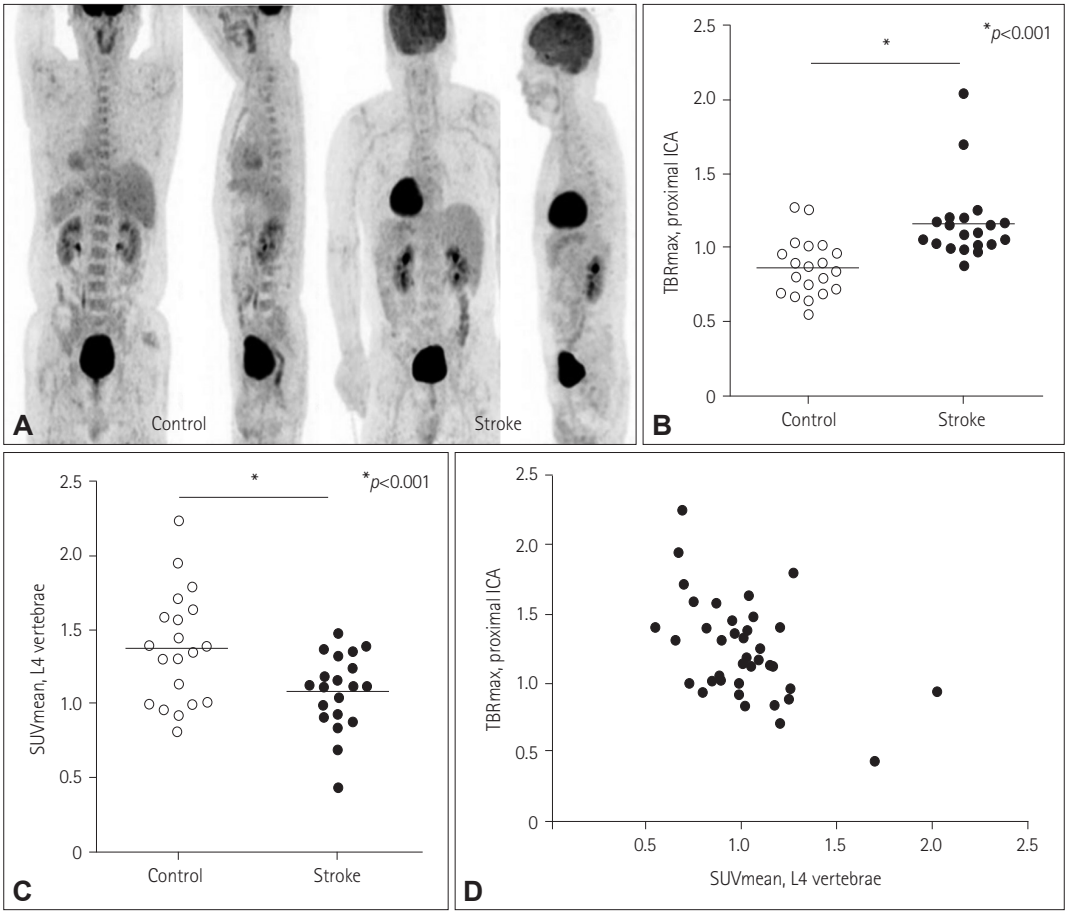

Fig. 1. Comparison of FDG uptake between control subjects and stroke patients. A: Representative coronal and sagittal whole-body FDG positron-emission tomography showing that FDG uptake in the vertebral bodies was lower in a stroke patient than a control subject. B: A comparison of FDG uptake in the proximal ICA between the two groups showed that FDG uptake was significantly higher in the stroke group than the control group (0.87±0.19 vs. 1.16±0.26; p<0.001 in t-test). C: However, stroke patients exhibited significantly lower FDG uptake in the lumbar vertebrae (1.38±0.38 vs. 1.09±0.26; p=0.007 in t-test). SUV, standardized uptake value. D: A correlation analysis revealed a significant negative correlation between FDG uptakes in the lumbar vertebrae and ICA (Pearson's correlation coefficient=-0.491, p=0.001). FDG: ^{18}F-fluorodeoxyglucose, ICA: internal carotid artery, L4: fourth lumbar vertebra, SUV: standardized uptake value, TBR: target-to-background ratio.

Table 2. Correlations between solid-organ ^{18}F-fluorodeoxyglucose uptakes and laboratory variables

	Age	BMI	WBC	Hematocrit	ALP	hsCRP	FBS	Liver SUV	L4 SUV	Spleen SUV
L4 SUV	-0.42 (0.007)	0.19 (0.23)	0.32 (0.04)	0.38 (0.02)	0.49 (0.001)	0.25 (0.12)	0.09 (0.96)	0.43 (0.005)		0.20 (0.23)
Liver SUV	-0.24 (0.14)	0.51 (0.001)	0.18 (0.28)	0.33 (0.04)	0.41 (0.01)	0.18 (0.28)	-0.07 (0.68)		0.43 (0.005)	0.68 (<0.001)
Spleen SUV	-0.06 (0.73)	0.49 (0.001)	0.22 (0.18)	0.24 (0.13)	0.21 (0.19)	0.05 (0.76)	-0.03 (0.84)	0.68 (<0.001)	0.20 (0.23)	

Data are Pearson's correlation coefficient (*p*) values.
ALP: alkaline phosphatase, BMI: body mass index, FBS: fasting blood sugar, hsCRP: high-sensitivity C-reactive protein, L4: fourth lumbar vertebra, SUV: standardized uptake value, WBC: white blood cell count.

Table 3. Results from bivariate linear regression analyses of ^{18}F-fluorodeoxyglucose uptake in the proximal internal carotid artery

	Unstandardized coefficient	Standardized error	Standardized coefficient	*p*
Age	0.010	0.003	0.435	0.005
Female	0.156	0.085	0.285	0.075
Hypertension	0.240	0.080	0.439	0.005
Diabetes mellitus	0.054	0.087	0.100	0.540
Stroke	0.295	0.073	0.549	<0.001
FBG	<0.001	0.001	0.105	0.518
hsCRP	0.003	0.003	0.155	0.339
Liver SUV	-0.268	0.118	-0.345	0.029
L4 SUV	-0.380	0.110	-0.491	0.001
Spleen SUV	-0.232	0.128	-0.282	0.078

FBG: fasting blood glucose, hsCRP: high-sensitivity C-reactive protein, L4: fourth lumbar vertebra, SUV: standardized uptake value.

Table 4. Results from multivariate linear regression analyses with proximal internal carotid artery ^{18}F-fluorodeoxyglucose uptake as a dependent variable

	Unstandardized coefficient	Standardized error	Standardized coefficient	*p*
Age	0.003	0.004	0.112	0.477
Hypertension	0.136	0.081	0.248	0.103
Stroke	0.124	0.094	0.230	0.196
L4 SUV	-0.243	0.113	-0.314	0.037

L4: fourth lumbar vertebra, SUV: standardized uptake value.

lated with FDG uptakes in the fourth lumbar vertebra and liver, but not with hsCRP or FDG uptake in the spleen (Table 3). Multivariate linear regression analysis demonstrated that the negative correlation between FDG uptakes in the lumbar vertebrae and proximal ICA remained significant after adjusting for age, hypertension, and stroke (standardized coefficient=-0.314, p=0.037) (Table 4). Another multivariate linear regression analysis with vertebral FDG level as a dependent variable showed that hematocrit was significantly correlated with vertebral FDG after adjusting for age and the presence of stroke (standardized coefficient=0.298, p=0.047) (Table 5).

Table 5. Results from multivariate linear regression analyses with vertebral ^{18}F-fluorodeoxyglucose uptake as a dependent variable

	Unstandardized coefficient	Standardized error	Standardized coefficient	*p*
Age	-0.005	0.005	-0.171	0.323
Stroke	-0.206	0.114	-0.297	0.079
Hematocrit	0.017	0.008	0.298	0.047

DISCUSSION

Studies investigating hematopoietic organ activity in patients with coronary artery disease have found marked elevations of FDG uptakes in the spleen and vertebrae, with this being associated with systemic inflammatory markers and future vascular events.[3,4] The present study showed that FDG uptake in the vertebrae was decreased in stroke patients with carotid atherosclerosis, suggesting the presence of a different pathophysiological mechanism compared with that of coronary artery disease. A previous study found that FDG uptake in the lumbar vertebrae was significantly lower in patients with asymptomatic intracranial atherosclerosis than in subjects without stroke.[7] Atherosclerosis is a chronic inflammatory condition of the vessel walls that is aggravated by the recruitment of inflammatory cells from hematopoietic organs, but the mechanistic interplay between hematopoietic organs and atherosclerosis may differ between the coronary and carotid arteries.

Multiple factors could be involved in the difference in the bone-vascular axis between stroke and myocardial infarction.[9] The mechanism underlying FDG uptake in the lumbar vertebrae is not precisely defined. Since there are various cell populations in bone, including hematopoietic/mesenchymal stem cells, osteoblasts, osteoclasts, and matrix-supporting cells, FDG uptake in the lumbar vertebrae might not be solely determined by the enhanced production and recruitment of inflammatory cells.[10,11] Comorbid medical conditions such as osteoporosis or immobilization after stroke might also influence FDG uptake in the lumbar vertebrae of the stroke patients. In addition, decreased FDG uptake may reflect the overall dysregulation of hematopoietic organ activity, considering the positive correlations of FDG uptake in the lumbar vertebrae with the serum hematocrit and WBC. The association

between FDG uptake in vertebrae and the hematocrit remained significant after adjusting for age and the presence of stroke. A defective hematopoietic stem-cell population may be associated with atherosclerosis progression and an impaired vascular regeneration capacity.[12,13] A recent study found that the clonal instability of bone-marrow stem cells was positively associated with future vascular events.[14] Further studies are required to determine whether vertebral FDG uptake is decreased in patients with a defective hematopoietic stem-cell population and/or niche within the bone marrow.

This study had several limitations. First, factors related to FDG uptake in the vertebrae of stroke patients were not fully disclosed, and so correlation analyses with osteoporosis, neurological severity, and medication profiles may be necessary to understand the mechanism underlying FDG uptake in bone. Second, the number of included patients was small and longitudinal information regarding stroke recurrence was not obtained, which restricts the ability to interpret the causal relationship between vertebral FDG uptake and atherosclerotic stroke. Third, this study was not able to identify the mechanistic mediator between decreased lumbar FDG uptake and increased FDG uptake in the wall of the ICA in stroke patients. Analyses of hematopoietic progenitor cell/inflammatory cell populations, microvesicles, and circulating microRNAs affecting both bone and vascular homeostasis might be helpful for elucidating the pathophysiological link between cerebral atherosclerosis and hematopoietic organs. We are currently recruiting more stroke patients to investigate bone mineral densities and blood samples with the aim of understanding the mechanism underlying vertebral FDG uptake and its impact on stroke recurrence.

This pilot study found that FDG uptake in vertebrae was significantly decreased in stroke patients and negatively correlated with FDG uptake in the ICA. Future studies are warranted to investigate the pathophysiological mechanism underlying decreased FDG uptake in solid organs and its prognostic implications for stroke patients.

Author Contributions

Conceptualization: Jeong-Min Kim, Kwang-Yeol Park. Data curation: Jeong-Min Kim, Eun Seong Lee. Formal analysis: Jeong-Min Kim, Eun Seong Lee. Funding acquisition: Jeong-Min Kim, Kwang-Yeol Park. Investigation: Jeong-Min Kim, Ju Won Seok. Methodology: Jeong-Min Kim, Ju Won Seok. Project administration: Jeong-Min Kim, Ju Won Seok. Resources: Jeong-Min Kim, Eun Seong Lee. Software: Jeong-Min Kim, Eun Seong Lee. Supervision: Kwang-Yeol Park, Ju Won Seok. Validation: Jeong-Min Kim, Eun Seong Lee, Ju Won Seok. Visualization: Jeong-Min Kim, Kwang-Yeol Park. Writing—original draft: Jeong-Min Kim, Kwang-Yeol Park. Writing—review & editing: Jeong-Min Kim, Kwang-Yeol Park, Ju Won Seok.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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