Background and Purpose  We investigated 18F-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.

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 18F-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 ¹⁸F-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/ml/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 the first 60 min and subsequently for 120 min, using 5 min/bed for the head and 1 min/bed for 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/m²           | 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, ×10⁹/L          | 6.7±2.1 | 7.3±1.6  | 0.397 |
| Hematocrit, %        | 41.1±5.6 | 39.7±7.0 | 0.510 |
| Platelet count, ×10⁹/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 sub-
jects 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 significant-
ly older and had a higher prevalence of hypertension and
diabetes mellitus (Table 1). Representative images and quan-
titative analysis showed that FDG uptake in the lumbar ver-
tebral 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 signifi-
cantly between the two groups (Table 1). The FDG uptake in
the lumbar vertebrae was negatively correlated with FDG up-
take in the proximal ICA (Pearson’s correlation coefficient =
-0.491, p = 0.001) (Fig. 1D).

Analysis of the correlations between solid-organ FDG up-
takes 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 correlat-
ed 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 corre-
lations 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-

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**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: 18F-fluorodeoxyglucose, ICA: internal carotid artery, L4: fourth lumbar vertebra, SUV: standardized uptake value, TBR: target-to-background ratio.
Decreased Bone FDG Uptake in Stroke Patients

활성화된 발수포에서 FDG 유입이 감소한다는 결과는 관상동맥질환 환자에서 관찰된 FDG 유입 증가와는 다르게, 이는 두 질환의 발병 기전이 다를 수 있다고 제안한다. 이전 연구에 따르면, 혈장 세포주변 섬유화 세포 활성화는 관상동맥질환 환자에서 관상동맥 FDG 유입이 감소하는 것으로 보고되었다. 7

연구 결과는 관상동맥질환과 비교하면, 관상동맥질환에서의 FDG 유입 감소는 관상동맥질환의 질환의 기전과는 달리, 관상동맥 질환의 발병 기전과 달라질 수 있다고 제안한다. 관상동맥질환의 경우, 관상동맥 FDG 유입 감소는 관상동맥질환의 활성화된 발수포에 따라 발생한다는 결과를 보여주고 있다. 8

## DISCUSSION

Studies investigating hematopoietic organ activity in patients with coronary artery disease have found marked elevations of FDG uptake 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.8 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.8,9 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

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

|                        | Age     | BMI     | WBC     | Hematocrit | ALP     | hsCRP   | FBS     | Liver SUV | L4 SUV | Spleen SUV |
|------------------------|---------|---------|---------|------------|---------|---------|---------|-----------|---------|------------|
| L4 SUV                 | -0.42   | 0.19    | 0.32    | 0.38       | 0.49    | 0.25    | 0.09    | 0.43      | 0.20    | 0.23       |
| Liver SUV              | -0.24   | 0.51    | 0.18    | 0.33       | 0.41    | 0.18    | -0.07   | 0.43      | 0.43    | 0.68 (<0.001) |
| Spleen SUV             | -0.06   | 0.49    | 0.22    | 0.24       | 0.21    | 0.05    | -0.03   | 0.68      | 0.20    | 0.23       |

Data are Pearson’s correlation coefficient (r) values.

Table 3. Results from bivariate linear regression analyses of 18F-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 18F-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.
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. A recent study found that the clonal instability of bone-marrow stem cells was positively associated with future vascular events. 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

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