Recently Uncontrolled Glycemia in Diabetic Patients Is Associated with the Severity of Intracranial Atherosclerosis

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Background and Purpose: Diabetes mellitus is a specific risk factor for intracranial atherosclerosis (ICAS) regardless of race. However, it is largely unknown whether poor glycemic control is associated with the severity of ICAS in diabetic patients. *Methods:* We selected diabetic patients with acute ischemic stroke who were prospectively registered between March 2005 and December 2015. The patients who had a high-risk source of cardiogenic embolism were excluded. ICAS was graded from 0 to 3 by the number of significant (≥50%) stenoses on intracranial magnetic resonance angiography, and was divided into 4 types: unilateral anterior, bilateral anterior, posterior, and anterior plus posterior. Ordinal and multinomial regression tests were applied for the factors influencing the number and types of ICAS. *Results:* A total of 774 patients with noncardioembolic acute ischemic stroke with diabetes were enrolled. The multiplicity of ICAS was independently associated with age (odds ratio [OR], 1.035 per 1 year, 1.018-1.052; $P < .001$), hypertension (OR, 1.992, 1.336-2.965; $P = .001$), and glycated hemoglobin (HbA1c; OR, 1.207 per 1%, 1.089-1.338; $P < .001$) in the ordinal regression model. In multinomial regression, bilateral anterior stenosis tended to be correlated with age (OR, 1.042, 1.008-1.077; $P = .016$) and HbA1c (OR, 1.201 per 1%, .991-1.520; $P = .057$). Both anterior and posterior stenoses were significantly associated with age (OR, 1.056, 1.029-1.084; $P < .001$), hypertension (OR, 2.584, 1.404-4.762; $P = .002$), and HbA1c (OR, 1.272, 1.070-1.511; $P = .006$). *Conclusions:* Age, concomitant hypertension, and HbA1c were factors associated with multiple intracranial stenoses. Further study is warranted to elucidate whether poor glycemic control facilitates ICAS in diabetic patients. **Key Words:** Diabetes—intracranial atherosclerosis—glycated hemoglobin—angiography.

Introduction

Intracranial atherosclerosis (ICAS) has been recognized as a major cause of stroke in the Asian population.[1,2] Among the risk factors for ICAS,[3-5] diabetes mellitus (DM) is specifically related to ICAS.[3,6] DM is independently associated with a higher number of diseased vessels and with greater extent of ICAS.[7] Patients with multiple ICAS had DM more often than those with single ICAS.[8] Diabetic patients with previous stroke have a higher resistance and alteration in intracranial blood vessels.[9,10]

In contrast, the role of glycemic control in the development of atherosclerotic cardiovascular disease for the patients with DM is less clear. A prospective, population-based study demonstrated the linear association of glycemic

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control with the risk for coronary heart disease in diabetic patients.[11] The serum levels of glycated hemoglobin were correlated with the severity of coronary artery disease in diabetic patients.[12,13] However, previous randomized clinical trials failed to provide consistent evidence for the effect of glycemic control on macrovascular disease. There was no difference in the incidence of atherosclerotic cardiovascular disease between the groups under intensive and standard glycemic control.[14-16]

There are several characteristics in risk factors, morphology, and mechanism that allow ICAS to be distinguished from extracranial atherosclerosis.[17] Intracranial arteries are less affected by hypercholesterolemia but have divergent atherogenic responses correlated with DM and the metabolic syndrome.[18,19] It is expected that ICAS could be more susceptible to blood glycemic control, but there are few studies about the influence of uncontrolled glycemia on the progression of ICAS. This study was designed to assess the relationship between recent glycemic control and the severity of ICAS in patients with DM.

Patients and Methods

Study Subjects

Among 2,737 patients with acute ischemic stroke or transient ischemic attack who were prospectively registered in a Soonchunhyang University medical center from March 2005 to December 2015, 1,049 (38.3%) had DM. Definitions of DM were (1) being diagnosed with diabetes and taking hypoglycemic agents before stroke; (2) 6.5 mg/dL of initial glycated hemoglobin or more; or (3) 126 mg/dL of fasting serum glucose or more.[20] Patients were excluded if they had a hemorrhagic stroke (n = 48); a high-risk source of cardiogenic embolism (n = 198); a stroke of other determined etiologies such as arterial dissection, vasculitis, Moyamoya disease, hematologic disorder, or coagulopathy (n = 47); no magnetic resonance angiography (MRA; n = 23); or incomplete workup for stroke etiology (n = 7). Finally, 744 patients with DM participated in the analysis. The study design was approved by the local Institutional Review Board before investigation (No. 2016-09-006).

Vascular Risk Factors and Other Variables

Data were collected including demographics, vascular risk factors, laboratory findings, and radiological findings in a web-based prospective registry.[21] We performed an extensive evaluation for the stroke mechanism in all patients: 95.8% for head and neck MRA, 90.3% for transthoracic echocardiography, and 86.7% for Holter monitoring.[22] High cardiogenic embolic sources included atrial fibrillation, valvular heart disease, sick sinus syndrome, cardiac myxoma, cardiomyopathy, and left ventricular akinesia or thrombus. Vascular risk factors included age, sex, body mass index (BMI), hypertension, current smoking, excessive alcohol intake, previous stroke or coronary heart disease, prestroke medications, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride. Serum lipid profiles were drawn the day after hospital admission, early in the morning after an overnight fasting with the last meal generally 12 hours before sampling. Hypertension was defined as a current use of antihypertensive medications or a high systolic blood pressure of 140 mmHg or higher, and/or a high diastolic blood pressure of 90 mmHg or higher 7 days after stroke. Excessive alcohol drinking was defined as average intake of more than 5 drinks (1 drink = 10 g of ethanol) per day.[23] We collected information about the history of diabetes with its duration from patients or caregivers on initial assessment. Glycated hemoglobin (HbA1c) was customarily checked using a Variant II Turbo analyzer (Bio-Rad, Hercules, CA) in all enrolled patients at admission.

Grading of Severity of Intracranial Arteries

All patients underwent conventional MRA on a 1.5-tesla system with echo-planar imaging capability (Sonata, Siemens Medical System, Erlangen, Germany) within 3 days of stroke onset. MRA data of intracranial arteries were retrospectively reviewed: distal internal carotid artery (ICA, cavernous and petrous segment), middle cerebral artery (MCA) M1 and M2 segments, anterior cerebral artery A1 and A2 segments, posterior cerebral artery P1 and P2 segments, basilar artery, and distal vertebral artery V4 segment. We determined the presence of intracranial stenosis on the 3-dimensional time-of-flight using a previously described method.[24] A diagnosis of significant (≥50%) intracranial stenosis was made by 2 investigators who were blinded to the infarction (N.R. Choi and J.Y. Lee) with good interobserver agreement ($\kappa = .853$), and the opinion of a third neuroradiologist (S.T. Park) in case of disagreement. Regardless of relevance to current stroke, the multiplicity of intracranial arterial stenosis was graded from 0 to 3 by the number of significant stenoses on MRA. The pattern of intracranial stenosis was divided into 4 types according to the involved vessels: unilateral anterior, bilateral anterior, posterior, and anterior plus posterior.

Statistical Analysis

The hypothesis being tested in this study was that poor glycemic control would have more severe intracranial stenosis. On the basis of an expected severe stenosis of 20% among euglycemic patients, we estimated that the enrollment of 780 patients would provide a statistical power of 80% to detect a relative increase of 10% in the fraction of severe stenoses among patients with poor glycemic control. Statistical analyses were performed using the SPSS software for Windows version 18.0 (IBM SPSS Statistics, Chicago, IL). Categorical variables are reported as frequencies, and continuous variables are reported as