Association Between Glycemic Control and Incident Stroke — Overview From an Epidemiologic Study —

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Diabetes is a major risk factor for cardiovascular disease, including stroke. However, the association between glycemic control and incident stroke is not sufficiently discussed in the non-diabetic population. In particular, the target value of glycemic control to prevent incident stroke is unclear. We summarize the results of epidemiological studies investigating the associations of markers for glycemic control with incident stroke and its subtypes.

The usual marker in the clinical setting for glycemic control is HbA1c, which reflects mean glucose levels over approximately 8–12 weeks. Previous epidemiological studies in several countries have reported that the HbA1c level is associated with ischemic stroke. The Atherosclerosis Risk in Communities (ARIC) study from the USA investigated the relationship between HbA1c and ischemic stroke in individuals with and without diabetes and found that the risk of ischemic stroke incidence continuously increased with HbA1c level. Furthermore, the European Prospective Investigation into Cancer (EPIC)-Norfolk prospective population study from the UK showed an exponential increased risk of stroke incidence or death from an HbA1c level of 7% as the threshold level. In Japan, a cohort study of 32,726 subjects aged 40–79 years in health checkups of Toyama City indicated that the adjusted hazard ratios of overall stroke and ischemic stroke increased with increasing HbA1c level, and additionally the relationships were independent of other confounders: however, HbA1c levels were not significantly associated with incident hemorrhagic stroke. Similarly, in the Hisayama Study of 2,851 participants aged 40–79 years, HbA1c levels were positively associated with the risk of ischemic stroke, but were not associated with hemorrhagic stroke. Several previous epidemiologic studies have revealed that HbA1c levels were associated with incident ischemic stroke, not hemorrhagic stroke. If there is a threshold for changing the association between HbA1c level and incident ischemic stroke, we could set the target value of HbA1c for the prevention of ischemic stroke. However, whether the association between HbA1c level and ischemic stroke has a threshold is still controversial.

In addition, participants in most of the previous studies that showed an association between HbA1c levels and ischemic stroke were under 80 years of age. The Leiden 85-plus study from the Netherlands investigated an association of HbA1c with incident stroke among 443 subjects aged 85 years without known diabetes during 5 years of follow-up. As a result, no association was found between HbA1c level and incident stroke. Thus, the association between HbA1c and incident stroke in advanced elderly people was not clarified. Further epidemiological study of advanced elderly people is expected in future.

There are several studies that have investigated the association between other markers of glycemic control and incident ischemic stroke. For example, pooled analysis of 237,468 individual participants’ data from 17 cohort studies in the Asia Pacific Cohort Studies Collaboration (APCSC) showed a 1 mmol/L (18 mg/dL) lower usual fasting glucose level was associated with a 21% lower risk of stroke consisting of fatal and non-fatal stroke. That study indicated that a 1 mmol/L (18 mg/dL) lower usual fasting glucose level was associated with a 17% lower risk of ischemic stroke incidence and death, but was not significant.

In this issue of the Journal, Imano et al investigated the associations of non-fasting glucose with incident stroke and its subtypes among 3,254 subjects aged 40–74 years from the Circulatory Risk in Communities (CIRCS) Study. The non-fasting glucose concentration was associated with greater risk of incident total strokes, ischemic stroke and lacunar infarction. On the other hand, in the APCSC, the association of usual non-fasting glucose concentration with overall stroke was weaker and less robust than that of usual fasting glucose concentration. However, in the APCSC, overall stroke included hemorrhagic stroke as well as ischemic stroke. Therefore, the true association between non-fasting glucose concentration and ischemic stroke might be weakened. Further study is needed to examine the association between non-fasting glucose and stroke and its subtypes.

The ARIC study investigated the associations of 1,5-AAG with incident ischemic stroke among 11,106 subjects...
without cardiovascular diseases over 20 years of follow-up. As a result, lower than 10 μg/mL of 1,5-AG was strongly associated with incident ischemic stroke. Similarly, the ARIC study investigated whether fructosamine or glycated albumin is the risk factor of incident ischemic stroke among 11,104 subjects without cardiovascular diseases over 20 years of follow-up, but neither was significantly associated with incident ischemic stroke. The reason why fructosamine or glycated albumin was not associated with ischemic incident stroke was not clarified, so we suppose that glycemic variation is not likely to be a risk for ischemic stroke in the population with good glycemic control.

There are several limitations in the previous epidemiological studies. First, the ascertainment of stroke and subtypes were not unified. For example, ischemic stroke is classified based on TOAST criteria in the Hisayama study, and incident ischemic stroke is defined based on self-reported questionnaire only in many epidemiological studies. Second, ECG abnormalities such as atrial fibrillation were not included as potential confounders in multivariate models, despite atrial fibrillation being one of the important risk factors of cardioembolic stroke. And also, the use of antiplatelet agents was an important confounder. Third, asymptomatic stroke or transient ischemic attack (TIA) was not measured in previous epidemiological studies. In general, lacunar infarction includes symptomatic lacunar infarction and asymptomatic lacunar infarction. TIA is also a major risk factor of stroke. Finally, in most previous studies, symptomatic stroke was set as the definition of incident stroke. However, determining the accurate date of stroke onset is difficult because not all stroke is symptomatic. Therefore, we have to evaluate the results of previous studies taking these facts into consideration.

In observational studies, glycemic control, including non-fasting glucose, has been associated with ischemic stroke, but not with hemorrhagic stroke. Furthermore, intervention for glycemic control only was not effective in preventing incident ischemic stroke in previous studies. Therefore, there is not enough evidence to elucidate whether glycemic control leads to prevention of cerebral infarction and further study is warranted.

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References