BACKGROUND AND PURPOSE: An increase in the common carotid artery intima-media thickness (CCA-IMT) is generally considered an early marker of atherosclerosis. This cross-sectional study assessed the CCA-IMT and plaque score as vascular risk factors in patients with ischemic stroke and type 2 diabetes.

MATERIALS AND METHODS: Brain MR imaging and carotid ultrasonography were performed in 133 subjects with type 2 diabetes. IMT was measured at both CCAs. Differences in the variables between case and control subjects were compared statistically. To determine the independent factors related to CCA-IMT and plaque score, we performed stepwise multiple regression analysis.

RESULTS: Sex, current smoking habit, history of hypertension, and high-density lipoprotein (HDL) levels differed significantly between the case and control groups. CCA-IMT and plaque score in patients with diabetes and acute ischemic stroke were significantly greater than in patients with diabetes who were stroke-free. The crude odds ratios suggested that CCA-IMT and plaque score are risk factors of acute ischemic stroke in patients with type 2 diabetes. However, when we adjusted for cerebrovascular risk factors, CCA-IMT and plaque score did not remain significantly associated with acute ischemic stroke.

CONCLUSION: Increased CCA-IMT and plaque score are associated with acute ischemic stroke in patients with type 2 diabetes. The higher CCA-IMT and plaque score found in ischemic stroke in patients with type 2 diabetes seem to be induced by cerebrovascular risk factors. Therefore, to prevent ischemic stroke in patients with type 2 diabetes, strict control of hyperglycemia, hypertension, smoking, and low HDL, together with monitoring of CCA-IMT and carotid plaque, may be important.
The traditional risk factors for cerebrovascular disease in both case and control subjects—age, sex, body mass index, history of hypertension, history of smoking, low-density and high-density lipoprotein (HDL) cholesterol levels, triglyceride levels, hemoglobin (Hb) A1c levels, and ischemic heart disease—were also evaluated. The survey on smoking was based on the participants’ recall. Smoking was defined as having at least 1 cigarette daily, as well as having smoked in the past. Nonsmoking was defined as self-reported lifetime abstinence.

**Brain MR Imaging**

All subjects underwent brain MR imaging. Patients with acute ischemic stroke underwent brain MR imaging within 2 days from the onset of symptoms. The median time between brain infarction and CCA-IMT evaluation was 8.1 days (range, 1–78 days) for case subjects and 7.5 days between brain MR imaging and CCA-IMT evaluation (range, 0–80 days) for control subjects. Diffusion-weighted, T1- and T2-weighted, and fluid-attenuated inversion recovery (FLAIR) images were obtained with a 1.5T Gyroscan Intera system (Philips, Bothell, Wash).

**Carotid Ultrasoundography**

We confined IMT measurements to the CCA because of the relatively common occurrence of plaques at the origin of the internal carotid artery (ICA). All case and control subjects underwent ultrasonography of both carotid arteries. CCA-IMT and plaque score were evaluated using high-resolution sonography equipped with a linear transducer at 7.5 MHz in B mode (HDI 5000 SonocT; Philips), and one neuroradiologist examined the results.

We assessed the presence of plaques in the CCA, bifurcation, and ICA, and defined plaques as focal widening of the vessel wall of more than 50% relative to adjacent segments, with protrusion into the lumen, composed of calcified or noncalcified components. Protrusion was visually determined. The total plaque score reflected the total number of sites with plaques and ranged from 0 to 6 (each of the CCAs, bifurcations, and ICAs, bilaterally). To access CCA-IMT, we focused on far-wall IMT, because far-wall measurements are considered to be more valid than near-wall measurements. IMT of the far wall was defined as the distance between the leading edge of the lumen-intima interface and the leading edge of the media-adventitia interface (Fig 1).

Far-wall IMT of both CCAs was measured at 3 sites (thickest point, and at sites 1 cm upstream and downstream, free from plaque) using Digital calipers (Mitutoyo, Kawasaki, Japan) on the longitudinal views. The maximum and mean IMT of the carotid arteries were assessed. The mean CCA-IMT was defined as the mean IMT of the right and left CCAs, calculated from 3 measurements on each side. The maximum CCA-IMT (max CCA-IMT) was defined as the average of the thickest wall of the right and left CCAs. If there was uniform intimal thickening in the CCA, we measured intimal thickness every 1 cm from the bifurcation to the end of the CCA. Then, we made 3 measurements: at the thinnest point and 1 cm upstream and downstream.

**Statistical Analysis**

IMT values were log transformed to obtain a normal distribution. Differences in variables between case and control subjects were analyzed for statistical significance by using the t test, Wilcoxon rank-sum test, x² test, and Fisher exact test. Multiple logistic regression analysis was performed to calculate the odds ratio of ischemic stroke associated with increased CCA-IMT and plaque score by adjusting for available risk factors of stroke.

**Results**

The baseline characteristics of the study subjects are shown in Table 1. Forty-four acute ischemic stroke cases were confirmed by imaging studies. They comprised 26 lacunar infarctions, 12 cortical infarctions, including territorial and border-zone infarctions, and 6 large subcortical infarctions. Significant differences were observed between the case and control groups in sex, current smoking habit, history of hypertension, and HDL levels.

The CCA-IMT (max IMT and mean IMT) and plaque score in the case subjects were higher than in control subjects (Table 2). In addition, the crude odds ratios suggested that CCA-IMT and plaque score were risk factors for acute ischemic stroke in patients with type 2 diabetes (Table 3). How-
We demonstrated that increased CCA-IMT and plaque score correlated with acute ischemic stroke in patients with type 2 diabetes. Sex, history of smoking, history of hypertension, and low HDL were statistically significant in the case subjects. However, after we adjusted for these 4 factors, CCA-IMT and plaque score did not remain significantly associated with acute ischemic stroke, indicating that CCA-IMT and plaque score are not independent cerebrovascular risk factors.

Although many studies have reported that CCA-IMT and plaque score are independent risk factors for ischemic stroke, even after adjusting for conventional risk factors, our results showed that CCA-IMT and plaque score were not independent factors for ischemic stroke. CCA-IMT is associated with modifiable (eg, blood pressure, blood cholesterol, smoking, diabetes, and obesity) and nonmodifiable risk factors (age, sex, genes, and currently unknown risk factors).

An increased carotid IMT has been observed in patients with type 2 diabetes. Diabetes itself might be of crucial importance for the development of atherosclerosis because of the clustering of various interrelated metabolic disturbances, as well as hyperglycemia. The cause of atherosclerosis in type 2 diabetes could be sought in the glucose toxicity to the endothelium and glycosylation processes, as indicated by the higher levels of plasma glucose and HbA1c in patients with diabetes, as well as in the significant increase in cardiovascular risk factors. Therefore, they emphasize that hyperglycemia and clustering of conventional risk factors are related to IMT. Kawamori et al reported that aging, hypertension, dyslipidemia, duration of diabetes, and smoking habits were related to CCA-IMT. Epidemiologic studies have reported associations between a range of cerebrovascular risk factors and IMT; Temelkova-Kurtzschief et al also reported a trend between a greater number of risk factors, and a thicker intima-media.

Hence, we argue that because IMT reflects exposure to cerebrovascular risk factors, IMT itself may not play a direct role in ischemic infarction and that it can be considered an intermediate factor in the causal pathway between clinical risk factors and stroke. Therefore, to prevent atherosclerosis of the carotid arteries in patients with type 2 diabetes, strict control of hypertension, hyperglycemia, smoking habits, and dyslipidemia seem to be important.

Therapeutic interventions with blood pressure-lowering agents and lipid-lowering agents, as well as multifactorial interventions in patients with diabetes, can slow the progression of or even reduce carotid IMT. Carotid IMT has been recently recognized as a surrogate marker for evaluating therapeutic interventions in atherosclerotic disease.

One limitation of our study is that it focused on acute stroke only and did not include diabetic subjects with chronic ischemic stroke or isolated transient ischemic attack (TIA). In future, the relationship between IMT and plaque score and ischemic stroke must be examined in all patients with diabetes, segregating them into patients with strokes (TIA, acute, and chronic) and without strokes.

**Conclusion**

Increased CCA-IMT and plaque score were correlated with acute ischemic stroke in patients with type 2 diabetes. How-
ever, the greater CCA-IMT and plaque score found in ischemic stroke for patients with type 2 diabetes seem to be induced by cerebrovascular risk factors prevalent in patients with diabetes, and CCA-IMT and plaque score seem to be vascular risk factors that reflect the degree of exposure to cerebrovascular risk factors. Therefore, CCA-IMT and plaque score in patients with type 2 diabetes can be considered intermediate factors in the causal pathway between cerebrovascular risk factors and ischemic stroke, not independent factors for ischemic stroke.

To prevent ischemic stroke in patients with type 2 diabetes, strict control of hyperglycemia, hypertension, smoking, and dyslipidemia, together with monitoring of CCA-IMT and carotid plaque, may be important. Large prospective studies are need to establish the link between earlier carotid atherosclerosis and the future stroke risk in patients with type 2 diabetes.

References