Correlation Between Common Carotid Arterial Wall Thickness and Ischemic Stroke in Patients With Type 2 Diabetes Mellitus

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If a strong association between intima-media thickness of the common carotid artery (CCA-IMT) and ischemic stroke can be determined in diabetic subjects, it may be a useful predictor to help identify patients at high risk of ischemic stroke. To investigate the relative contribution of CCA-IMT to ischemic stroke in patients with type 2 diabetes, we measured CCA-IMT and other conventional risk factors in 438 Japanese patients with type 2 diabetes, including 45 with ischemic stroke and 393 controls. Stroke patients were characteristically and significantly older with higher body mass index, longer duration of diabetes, likely to be smokers, higher blood pressure, and higher total cholesterol compared with the controls. CCA-IMT in stroke patients (1.23 ± 0.04 mm) was significantly greater than in control patients (0.95 ± 0.01 mm, *P* < .01). CCA-IMT in stroke patients was still significantly greater than controls after adjustment for age, sex, body mass index, and smoking status (*P* < .05). A 0.1-mm increase in CCA-IMT was associated with 1.80-fold increase in the odds ratio of stroke in diabetic patients (95%confidence interval [CI], 1.49 to 2.17; *P* < .01). Four independent factors were found to correlate significantly with CCA-IMT: age, systolic blood pressure, HbA_{1c}, and high-density lipoprotein (HDL) cholesterol. Thus, thickening of the intima-media of common carotid arteries is associated with ischemic stroke in type 2 diabetic patients. To prevent ischemic stroke, strict control of diabetes, hypertension, and dyslipidemia and monitoring of CCA-IMT may be important.

NONINVASIVELY MEASURED thickness of the intima-media layers of common carotid arteries (CCA-IMT) has been recently used as a marker for early atherosclerosis.[1-3] Increased CCA-IMT has been reported in various conditions, such as hypertension, obesity, diabetes, and cardiovascular disease, including ischemic stroke.[4-8]

Type 2 diabetes is an important risk factor for atherosclerotic diseases such as coronary artery disease, stroke, and peripheral vascular obstructive disease.[9-11] Previous studies have indicated that Japanese patients with type 2 diabetes are more likely to develop stroke but less likely to have coronary artery disease compared with Caucasians.[12,13] Furthermore, the population-based Hisayama study concluded that the relative risk of ischemic stroke in Japanese patients with type 2 diabetes was 3-fold that in subjects with normal glucose tolerance.[14] Because ischemic stroke is associated with atherosclerosis of intra- and extracranial arteries, increased CCA-IMT may be present in such state. In fact, increased CCA-IMT was recently demonstrated in patients with type 2 diabetes.[15] To our knowledge, however, no studies have specifically investigated the relationship between ischemic stroke and CCA-IMT in type 2 diabetes. Furthermore, the majority of similar studies did not stratify stroke into ischemic stroke, cerebral hemorrhage, and cardioembolic infarction.[7,8,16]

In the present study, we evaluated the relative contribution of increased CCA-IMT on ischemic stroke in Japanese patients with type 2 diabetes. We also evaluated the metabolic factors related to CCA-IMT in the same patients.

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SUBJECTS AND METHODS

Type 2 diabetic patients with acute ischemic stroke or a history of ischemic stroke who visited Sasebo Chuo Hospital were consecutively recruited between December 1998 and July 2000. Type 2 diabetes was diagnosed by the 1998 criteria of World Health Organization. The diagnosis of ischemic stroke was based on the following: (1) presence of clinical symptoms of stroke, (2) no cerebral bleeding on computed tomography, and (3) presence of infarction confirmed by magnetic resonance imaging. Patients with stroke due to cardioembolic origin were excluded. Control patients with type 2 diabetes but without a history of stroke were consecutively recruited during the same period. A total of 438 patients with type 2 diabetes, including 45 with ischemic stroke and 393 controls, were included in this cross-sectional study. Informed consent was obtained from each patient, and the study protocol was approved by the ethics committee of Sasebo Chuo Hospital.

CCA-IMT was measured with high-resolution B-mode ultrasonography (SSA-340A, Toshiba, Tokyo, Japan) with an electronic linear transducer (mid-frequency, 8 MHz). CCA-IMT value was determined as originally described by Pignoli et al.[1] Briefly, far wall IMT of both common carotid arteries was measured at 3 determinations (greatest thickness point, 1 cm upstream, and 1 cm downstream) in anterior oblique, lateral, and posterior oblique longitudinal views. The mean value of the 18 IMT values of both common carotid arteries was used as a measure of CCA-IMT. Localized thickness of more than 2.0 mm was considered as plaque and excluded from the analysis.[17,18]

Patients with acute strokes were examined after their clinical conditions stabilized (rehabilitation state). Patients with a past history of ischemic stroke were examined in the outpatient department. Postprandial blood samples were obtained 2 hours after a standard breakfast on the day of ultrasonography of CCA. Glycosylated HbA_{1c}, total cholesterol, triglyceride, and high-density lipoprotein (HDL) cholesterol were measured in each patient using standard procedures.

Statistical Analysis

Differences in continuous variables between stroke and control patients were examined for statistical significance using the Student's *t* test. The categorical variables were analyzed using contingency tables. Analysis of covariance (ANCOVA) with contrasts was used to compare CCA-IMT after adjustment for age, sex, body mass index, and smoking habits. Multiple logistic regression analysis was performed to calculate the odds ratio of ischemic stroke associated with increased CCA-IMT. The relationship between CCA-IMT and other continuous variables was examined by Pearson's correlation analysis. To determine the independent factors related to CCA-IMT, we performed stepwise multiple regression analysis. A forward stepwise regression was selected with a cutoff level of significance of .05. Data are presented as the mean ± SEM. Differences were considered statistically significant at $P < .05$. Statistical analysis was performed with the SPSS 6.1 or Super ANOVA (Abacus, Berkeley, CA) statistical package.

RESULTS

Clinical Characteristics of Patients

The clinical characteristics of ischemic stroke and control patients are presented in Table 1. Stroke patients were significantly older, had a higher body mass index, longer history of diabetes, and were more likely to be smokers than control patients. Furthermore, the systolic blood pressure and postprandial total cholesterol levels were significantly higher in stroke patients than controls. On the other hand, the percentage of patients on insulin therapy and the levels of glycosylated HbA_{1c}, postprandial triglyceride, and HDL cholesterol were comparable to controls. CCA-IMT was significantly greater in ischemic stroke patients than controls, even after adjustment for age, sex, body mass index, and smoking habits (adjusted CCA-IMT: 1.22 ± 0.04 and 0.96 ± 0.01 mm; $P < .05$, respectively, ANCOVA).

Relationship Between CCA-IMT and Stroke

Figure 1 shows the prevalence of ischemic stroke according to the quartile of CCA-IMT. The proportion of patients with type 2 diabetic and ischemic stroke increased with larger CCA-IMT. Multiple logistic regression analysis showed that a 0.1-mm increase in CCA-IMT was associated with 1.80-fold increase in the odds ratio of stroke (95% confidence interval [CI], 1.49 to 2.17; $P < .01$) after adjustment for the variables listed in Table 1. These results indicate that increased CCA-IMT correlated significantly with ischemic stroke in patients with type 2 diabetes.

Table 1. Clinical Characteristics of Type 2 Diabetic Patients With Ischemic Stroke and Those Without Stroke (Control)

Characteristic	Stroke Patients	Control Patients
No. (male/female)	45 (33/12)	393 (229/164)
Age (yr)	67.1 ± 1.3†	61.8 ± 0.5
Body mass index (kg/m^2)	24.6 ± 0.5*	23.5 ± 0.2
Duration of diabetes (yr)	9.6 ± 1.0*	7.4 ± 0.3
Smoking habits [n (%)]	26 (57.8)†	127 (32.2)
Insulin therapy [n (%)]	13 (28.9)	86 (21.9)
Systolic blood pressure (mm Hg)	143 ± 2†	134 ± 1
Diastolic blood pressure (mm Hg)	78 ± 2	76 ± 2
HbA_{1c} (%)	7.5 ± 0.3	7.1 ± 0.1
Total cholesterol (mmol/L)	5.33 ± 0.20*	4.99 ± 0.05
Triglyceride (mmol/L)	1.75 ± 0.18	1.65 ± 0.06
HDL cholesterol (mmol/L)	1.44 ± 0.07	1.50 ± 0.02
CCA-IMT (mm)	1.23 ± 0.04†	0.95 ± 0.01

*$P < .05$ *v* control.
†$P < .01$ *v* control.

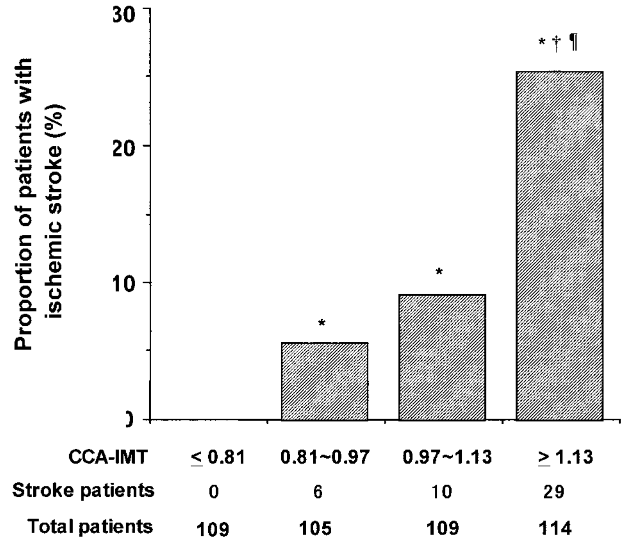

Fig 1. Relationship between quartile of CCA-IMT and proportion of type 2 diabetic patients with ischemic stroke. *$P < .05$ *v* lowest quartile (CCA-IMT, ∼0.81 mm). †$P < .05$ *v* second quartile (CCA-IMT, 0.81-0.97 mm). ¶$P < .05$ *v* third quartile (CCA-IMT, 0.97-1.13 mm).

Relationship Between CCA-IMT and Other Metabolic Variables

As shown in Table 2, CCA-IMT correlated significantly with age, duration of diabetes, systolic blood pressure, and HbA_{1c} levels. CCA- IMT significantly and inversely correlated with HDL cholesterol levels. To determine the independent factors that significantly correlated with CCA-IMT, we performed stepwise multiple regression analysis. The independent variables used in this analysis were those listed in Table 2. Our model found that age, systolic blood pressure, HbA_{1c}, and HDL cholesterol were independent and significant factors that correlated with ischemic stroke in patients with type 2 diabetic (Table 3).

DISCUSSION

The association between CCA-IMT and stroke has been reported in previous studies.[7,8,16,17,19] However, none of these studies examined diabetic patients only. Furthermore, most studies did not distinguish between ischemic stroke and cere-

Table 2. Correlation Coefficients Between CCA-IMT and Continuous Variables in Type 2 Diabetic Patients

Parameter	Correlation Coefficient	*P* Value
Age	0.48	<.001
Body mass index	0.07	.143
Duration of diabetes	0.28	<.001
Systolic blood pressure	0.34	<.001
Diastolic blood pressure	0.05	.348
HbA_{1c}	0.14	.003
Total cholesterol	0.04	.357
Triglyceride	0.06	.194
HDL cholesterol	−0.12	.015

Table 3. Independent Variables That Correlated Significantly with CCA-IMT Based on Stepwise Multiple Regression Analysis in Type 2 Diabetic Patients

Variable	β	SE
Age	0.42	0.001
Systolic blood pressure	0.25	0.0005
HbA_{1c}	0.10	0.006
HDL cholesterol	−0.10	0.021

Model $R^2 = 0.31$, $F = 49.1$, $P < .001$

bral hemorrhage or cardiogenic embolism.[7,8,16] In the present study, we focused on patients with type 2 diabetes, and excluded those with stroke due to brain hemorrhage and cardiogenic embolism.

Our results demonstrated that ischemic stroke correlated with CCA-IMT in Japanese patients with type 2 diabetes. CCA-IMT in diabetic patients with ischemic stroke was significantly greater than stroke-free diabetic patients, and the prevalence of ischemic stroke increased with increased CCA-IMT. This association was still significant after adjustment for conventional risk factors. The conventional risk factors of ischemic stroke are well known. The United Kingdom Prospective Diabetes Study[20] identified aging, male sex, hypertension, and atrial fibrillation as significant risk factors related to stroke. In Japanese patients with type 2 diabetes, aging, hypertension, duration of diabetes, hyperglycemia, dyslipidemia (high low-density lipoprotein [LDL] and low HDL), and smoking habits were identified as significant risk factors for stroke.[13] In our study, aging, increased adiposity, duration of diabetes, smoking habits, hypertension, and hyperlipidemia were significantly related to clinical ischemic stroke. Together, these results suggest that aging and clustering of conventional risk factors including hypertension correlate with ischemic stroke in diabetic patients. These clinical characteristics are known as insulin resistance syndrome.[21,22] In fact, we have reported previously that insulin resistance per se was significantly and independently related to ischemic stroke in patients with type 2 diabetes.[23] However, clinical identification of patients at risk for ischemic stroke is difficult because most patients with type 2 diabetes have overlapping metabolic abnormalities. Furthermore, exact measurement of insulin resistance such as glucose clamp and minimal model analysis is complicated to use in clinical examination.

Measurement of CCA-IMT is considered to reflect the presence of atherosclerosis, and is easy to use in clinical practice. In a French multi-neurological center study, Touboul et al[19] reported that increased CCA-IMT was associated with ischemic stroke. In their study, the odds ratio per 1 SD (0.15 mm) increase in CCA-IMT was 1.73. In our study, similar results were found when we restricted our population sample to patients with type 2 diabetes; the odds ratio per 0.10-mm increment in CCA-IMT was 1.80. Thus, a measurement of CCA-IMT may be clinically useful for identification of patients at high risk for ischemic stroke.

Our study identified aging, duration of diabetes, systolic blood pressure, HbA_{1c}, and HDL cholesterol as risk factors related to CCA-IMT in Japanese patients with type 2 diabetes. Further examination of our data using multivariate analysis showed that aging, systolic blood pressure, HbA_{1c}, and HDL cholesterol were independently related to CCA-IMT. These results are similar to those reported by other investigators. For example, Kawamori et al[2] reported that aging, hypertension, dyslipidemia, duration of diabetes, and smoking habits were related to CCA-IMT. Furthermore, Temelkova-Kurktschiev et al[24] also reported that hyperglycemia and clustering of conventional risk factors were related to IMT. Thus, to prevent atherosclerosis of the carotid arteries, strict control of hypertension, hyperglycemia, and dyslipidemia seems to be important in patients with type 2 diabetes.

There are several limitations in the present study. First, the relationship between CCA-IMT and ischemic stroke was estimated by a cross-sectional design. Therefore, we could not demonstrate any direct and time-dependent causal relationship between CCA-IMT and the development of ischemic stroke. Second, our study relied on a clinic-based method. Thus, our results could not be applicable to all Japanese patients with type 2 diabetes. Furthermore, ischemic stroke patients who died before hospitalization could not be recruited in our study, and thus the association of CCA-IMT and ischemic stroke may be under- or overestimated. To confirm the significance of CCA-IMT in ischemic stroke, longitudinal studies of patients with type 2 diabetes are necessary.

In conclusion, we have demonstrated that increased thickness of the intima-media layer of the common carotid arteries correlated with ischemic stroke in Japanese patients with type 2 diabetes. Furthermore, we also showed that aging, systolic hypertension, hyperglycemia, and low HDL cholesterol were independently related to CCA-IMT. To prevent ischemic stroke, strict control of diabetes, hypertension, and dyslipidemia, together with monitoring of CCA-IMT, may be important.

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