Poor glycemic control and posterior circulation ischemic stroke

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Abstract

Background

This study aimed at determining whether diabetes or glucose metabolism is associated with ischemic stroke in the posterior circulation.

Methods

We included 10,245 patients with acute ischemic stroke (mean age 72.7 ± 12.5 years, men 59.5%) who were enrolled in a multicenter hospital-based stroke registry in Fukuoka, Japan, between June 2007 and August 2016. Posterior circulation ischemic stroke (PCIS) was defined as brain infarction in the territory of the posterior cerebral artery and vertebro-basilar arteries. We investigated the associations between diabetes or glycemic parameters, including plasma glucose concentrations, hemoglobin A1c, and the homeostatic model assessment of insulin resistance (HOMA-IR), and PCIS using logistic regression analysis. To improve covariate imbalance, we further evaluated associations after propensity score matching using 1:1 nearest neighbor matching and inverse probability weighting.

Results

Diabetes was significantly associated with PCIS even after adjusting for multiple confounding factors (odds ratio—OR [95% confidence interval], 1.37 [1.25–1.50]). Similarly, fasting (1.07 [1.02–1.12]/SD), casual plasma glucose (1.16 [1.11–1.20]/SD) concentrations, and hemoglobin A1c (1.12 [1.08–1.17]/SD), but not HOMA-IR (1.02 [0.97–1.07]/SD), were associated with PCIS. These associations were maintained in patients with ischemic stroke because of thrombotic etiology and were unchanged even after the propensity score matching methods. In patients with diabetes, the ORs of PCIS further increased with an increase in hemoglobin A1c and the presence of microvascular complications.

Conclusions

Poor glycemic control may be associated with an increased risk of thrombotic infarction that occurs preferentially in the posterior circulation of the brain.

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A fifth of ischemic strokes affect structures in the posterior circulation of the brain, such as the brain stem and cerebellum.^{1,2} The clinical features of posterior circulation ischemic stroke (PCIS) and anterior circulation ischemic stroke differ in some respects.^{3,4} PCIS is sometimes difficult to diagnose, because the clinical symptoms of PCIS, such as dizziness, vertigo, and nausea, appear atypical of the focal neurologic signs in stroke. Moreover, CT is of limited diagnostic use for PCIS. Therefore, clinicians should consider underlying PCIS when nonspecific neurologic symptoms develop in patients with cardiovascular risk factors.

Diabetes is a well-established risk factor for ischemic stroke.⁵ Previous studies have suggested that diabetic patients suffer PCIS more frequently than nondiabetic patients.⁶⁻¹² There may be physiologic and histopathologic differences between anterior and posterior circulations. Some studies have suggested that posterior brain arteries have reduced vaso-reactivity,¹³ thinner walls, less elastin, and more concentric intima thickening¹⁴ compared with anterior brain arteries. However, it is still uncertain whether the posterior circulation is actually more vulnerable to ischemia than the anterior circulation in diabetic patients. Moreover, it remains to be determined how glucose metabolism is associated with a greater risk of PCIS.

To address these issues, we investigated the relationship between glycemic parameters and the vascular territory of infarct lesions in patients with acute ischemic stroke who were enrolled in a large-scale, prospective, hospital-based registry in Fukuoka, Japan. Thus, this study aimed at clarifying the relationship between diabetes or glucose metabolism and the development of PCIS.

Methods

Standard protocol approvals, registrations, and patient consents

The Fukuoka Stroke Registry is a multicenter, hospital-based registry of acute stroke patients. Kyushu University Hospital and 6 stroke centers (National Hospital Organization Kyushu Medical Center, National Hospital Organization Fukuoka-Higashi Medical Center, Fukuoka Red Cross Hospital, St. Mary's Hospital, Steel Memorial Yawata Hospital, and the Japan Labor Health and Welfare Organization Kyushu Rosai Hospital) in Fukuoka, Japan, participate in this registry. Detailed information about the study design, data collection, and harmonization in the registry has been described previously.^{15,16} The institutional review boards of the ethics committees in all the hospitals approved the study design. Written informed consent was obtained from all patients or family members. All patients underwent brain CT, magnetic resonance imaging, or both, during hospitalization. Stroke was defined as the sudden onset of a nonconvulsive and focal neurologic deficit on the basis of brain imaging findings.

Study participants

From June 2007 to August 2016, we enrolled 11,157 patients with acute ischemic stroke in the Fukuoka Stroke Registry. Of these, we excluded 512 patients whose symptoms lasted for less than 1 hour and 400 patients whose acute infarct lesion could not be identified by diffusion-weighted imaging. Thus, 10,245 patients with acute ischemic stroke were included in the final analysis (figure 1).

Clinical assessments

We investigated the clinical characteristics of the patients, such as age, sex, cardiovascular risk factors, body mass index, and previous stroke, on admission. Cardiovascular risk factors included hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg in the chronic stage, or compatible medical history and pre-admission treatment with antihypertensives), dyslipidemia (low-density lipoprotein cholesterol ≥ 3.62 mmol/L, high-density lipoprotein cholesterol < 1.03 mmol/L, triglycerides ≥ 1.69 mmol/L, or pre-admission use of cholesterol-lowering drugs), atrial fibrillation (during hospitalization or previously), smoking habits (both previous and current), drinking habits (habitual consumption of alcoholic beverages), coronary artery disease (history of angina pectoris, coronary revascularization, myocardial infarction, or bypass surgery for coronary artery disease), and chronic kidney disease (an estimated glomerular filtration rate¹⁷ of < 60 mL/min/1.73 m²). Body mass index was calculated as weight (kg)/(height [m])² on admission. Previous stroke was defined as a previous history of ischemic or hemorrhagic stroke.

Stroke was categorized into small vessel occlusion, large artery atherosclerosis, cardioembolism, and other subtypes on admission, according to the classification system used in the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study.¹⁸ Thrombotic stroke was defined as ischemic stroke because of small vessel occlusion or large artery atherosclerosis.

Diabetes and glycemic parameters

To assess glucose metabolism, we measured fasting plasma glucose (FPG), casual plasma glucose (CPG), fasting immunoreactive insulin (IRI), and hemoglobin A1c (HbA1c) during hospitalization. Insulin resistance was assessed by calculating the homeostatic model assessment for insulin resistance (HOMA-IR): $\text{FPG (mg/dL)} \times \text{fasting IRI (mU/L)} / 405$.¹⁹ Blood samples were collected in the fasting state or at random times with respect to food consumption within 10 days at a mean $\pm$ SD of 2.1 ± 1.4 days after admission. Diabetes mellitus was diagnosed on the basis of a previous history of diabetes or according to the diagnostic criteria of the Japan Diabetes Society during the postacute stage of stroke (> 3 weeks after stroke onset). The diagnosis was made by confirmation of chronic hyperglycemia (FPG ≥ 7.0 mmol/L, 2-hour post-load glucose ≥ 11.1 mmol/L during a 75 g oral glucose tolerance test, CPG ≥ 11.1 mmol/L, or HbA1c $\geq 6.5\%$) and/or the presence of typical symptoms of

Figure Flow chart for patient selection

diabetes mellitus (e.g., dry mouth, polydipsia, polyuria, and body weight loss) or a diagnosis of diabetic retinopathy.²⁰

The diabetic microvascular complications included retinopathy, nephropathy, and neuropathy. The diagnosis of these complications was made on the basis of previous history before stroke onset or the findings during hospitalization, adjudicated by the steering committee members. Retinopathy was diagnosed according to the findings of funduscopy, if available. Nephropathy included overt nephropathy, kidney failure, or continued dialysis, following the criteria proposed by the Japan Diabetes Society.²¹ Neuropathy included peripheral neuropathy, autonomic neuropathy, and other diabetes-related neuropathy.

Posterior circulation ischemic stroke

The primary outcome of this study was PCIS that was diagnosed on the basis of brain imaging. We categorized infarct lesions according to the arterial territory affected: the internal carotid artery, middle cerebral artery, anterior cerebral artery, posterior cerebral artery, or vertebro-basilar artery system. Then, infarcts in the territories of the internal carotid artery, middle cerebral artery, or anterior cerebral artery were defined as anterior circulation infarcts, and those in the territories of the posterior cerebral artery or vertebro-basilar artery were defined as posterior circulation infarcts, i.e., PCIS. Infarction involving the border zone between the anterior and posterior circulations, such as in the watershed between the middle cerebral artery and posterior cerebral artery, was included as PCIS. Multiple infarcts involving both posterior and anterior circulations were also regarded as PCIS.

Statistical analysis

Clinical characteristics were compared between patients with and without diabetes mellitus by the unpaired *t* test, Mann–Whitney *U* test, or χ^2 test, as appropriate. Age- and sex-adjusted or multivariable-adjusted odds ratio (OR) and 95% confidence interval (CI) of PCIS were estimated using logistic regression analysis. The multivariable model included age, sex, hypertension, dyslipidemia, atrial fibrillation, smoking, drinking, body mass index, chronic kidney disease, coronary artery disease, previous stroke, and stroke subtypes. HbA1c values were graded into 4 groups according to the criteria of the Japan Diabetes Society as follows: G1 < 6.0%, G2 6.0%–6.9%, G3 7.0%–7.9%, G4 ≥ 8.0%.²² Other glycemic parameters were categorized into quartiles. The OR and 95% CI for each category of FPG, CPG, HOMA-IR, and HbA1c were estimated by reference to the lowest category. OR and 95% CI were also estimated per 1 SD of FPG, CPG, HbA1c, and log-transformed HOMA-IR.

We additionally performed propensity score matching to control the covariates. The probability of diabetes (i.e., propensity score) was calculated for patients with and without diabetes using a logistic regression model. For calculation of the propensity score, we used 12 covariates, including age, sex, hypertension, dyslipidemia, atrial fibrillation, smoking, drinking, body mass index, chronic kidney disease, coronary artery disease, previous stroke, and stroke subtype. We first matched diabetic patients with nondiabetic patients by 1:1 nearest neighbor (Greedy-type) matching of the SD of the logit of the propensity score with a caliper width of 0.20. After propensity

The prevalence of hypertension, dyslipidemia, smoking, chronic kidney disease, coronary artery disease, and previous stroke were higher in diabetic patients than in nondiabetic patients.

score matching without replacement, diabetic and nondiabetic patients who met the matching criteria were selected. Consequently, the range of the standardized percentage bias in covariates was reduced after matching from 4.0%–34.4% to 0.1%–1.8% in all patients and from 4.3%–31.4% to 0.0%–2.5% in patients with thrombotic stroke. ORs of PCIS in the propensity score-matched cohort were estimated using conditional logistic regression analysis. To estimate the effect of exposure variables, such as diabetes, FPG, CPG, HbA1c, and HOMA-IR, on PCIS in the overall cohort, the inverse probability weighted method was used. We calculated the propensity score for diabetes or glycemic parameters and estimated average treatment effects of the variables on PCIS after weighting by the inverse of the probability.

We calculated the E value to estimate how the reported adjusted OR might change if unmeasured covariates could be accounted for.²³ In sensitivity analysis, we investigated the associations only in patients who had been diagnosed with diabetes mellitus. All of the statistical analyses were performed using Stata 14.0 software (StataCorp LP, College Station, TX) and SAS 9.4 software (SAS Institute Inc., Cary, NC). Two-sided probability values < 0.05 were considered to be statistically significant.

Data availability

Anonymized data will be shared by request from any qualified investigator.

Results

Clinical characteristics of patients with and without diabetes

The mean (SD) age of the patients was 72.7 (12.5) years, and 40.5% were women. Of all the patients, 3,264 (31.9%) patients were diagnosed as having diabetes mellitus. The diabetic patients were younger and had higher body mass indexes than the nondiabetic patients (table 1). The prevalence of hypertension, dyslipidemia, smoking, chronic kidney disease, coronary artery disease, and previous stroke were higher in diabetic patients than in nondiabetic patients. In contrast, female sex and atrial fibrillation were less prevalent in diabetic patients than in nondiabetic patients. Diabetic patients more often had a thrombotic stroke than nondiabetic patients.

Table 1 Background characteristics of patients with and without diabetes mellitus

	No diabetes n = 6,981	Diabetes n = 3,264	p Value
Age, y, mean ± SD	73.4 ± 13.1	71.4 ± 10.9	<0.001
Female, n (%)	3,075 (44.1)	1,079 (33.1)	<0.001
Risk factors, n (%)			
Hypertension	5,388 (77.2)	2,827 (86.6)	<0.001
Dyslipidemia	3,267 (46.8)	2,050 (62.8)	<0.001
Atrial fibrillation	1,998 (28.6)	659 (20.2)	<0.001
Smoking	3,491 (50.0)	1,897 (58.1)	<0.001
Drinking	2,442 (35.0)	1,080 (33.1)	0.06
Body mass index, kg/m², mean ± SD	22.4 ± 3.7	23.7 ± 3.9	<0.001
Comorbidity, n (%)			
Chronic kidney disease	2,554 (36.6)	1,297 (39.8)	0.002
Coronary artery disease	883 (12.7)	674 (20.7)	<0.001
Previous stroke, n (%)	1,402 (20.1)	834 (25.6)	<0.001
Stroke subtype, n (%)			
Thrombotic stroke	3,032 (43.7)	1,869 (57.4)	<0.001
Small vessel occlusion	1,970 (28.4)	1,079 (33.1)	
Large artery atherosclerosis	1,062 (15.3)	790 (24.3)	
Cardioembolic stroke	1,871 (26.9)	527 (16.2)	
Others	2,040 (29.4)	859 (26.4)	

Glycemic parameters, including FPG, CPG, fasting IRI, HbA1c, and HOMA-IR, were higher in diabetic patients (FPG, mean [SD]: 143.9 [50.0] mg/dL; CPG, mean [SD]: 185.3 [77.6] mg/dL; fasting IRI, median [interquartile range]: 6.5 [4.0–10.7] μU/mL; HbA1c, mean [SD]: 7.6% [1.6%]; HOMA-IR, median [interquartile range]: 2.1 [1.2–3.9]) than in nondiabetic patients (FPG: 103.1 [23.4] mg/dL, $p < 0.001$; CPG: 118.1 [28.4] mg/dL, $p < 0.001$; fasting IRI: 6.3 [4.1–10.1], $p = 0.03$; HbA1c: 5.7% [0.4%], $p < 0.001$; HOMA-IR: 1.5 [1.0–2.6], $p < 0.001$).

Associations between diabetes or glucose metabolism and posterior circulation ischemic stroke

PCIS was more frequent in diabetic patients (38.5%) than in nondiabetic patients (30.4%, $p < 0.001$, table 2, table e-1, links.lww.com/CPJ/A80). Because the factors confounding the relationship between glycemic control and PCIS were similar to those between diabetes and PCIS (table e-2), we adjusted for these covariates using logistic regression analysis. Consequently, even after adjusting for multiple confounding factors, the OR of PCIS was significantly higher in diabetic patients compared with nondiabetic patients (table 2).

Table 2 Associations between diabetes or glycemic parameters and PCIS

	PCIS (%)	Multivariable-adjusted		
		OR	(95% CI)	<i>p</i> Value
Diabetes				
Nondiabetes, n = 6,981	2,122 (30.4)	1.00	(Reference)	
Diabetes, n = 3,264	1,255 (38.5)	1.37	(1.25–1.50)	<0.001
FPG				
Q1 (FPG <93, mg/dL), n = 2,159	698 (32.3)	1.00	(Reference)	
Q2 (93 ≤ FPG <104.5, mg/dL), n = 2,223	731 (32.9)	1.00	(0.88–1.14)	0.99
Q3 (104.5 ≤ FPG <126, mg/dL), n = 2,168	689 (31.8)	0.97	(0.85–1.10)	0.62
Q4 (126 ≤ FPG, mg/dL), n = 2,216	801 (36.2)	1.15	(1.01–1.30)	0.04
<i>p</i> For trend				0.06
Per 1 SD		1.07	(1.02–1.12)	0.004
CPG				
Q1 (CPG <103, mg/dL), n = 2,429	707 (29.1)	1.00	(Reference)	
Q2 (103 ≤ CPG <121, mg/dL), n = 2,665	799 (30.0)	1.05	(0.93–1.18)	0.48
Q3 (121 ≤ CPG <155, mg/dL), n = 2,537	825 (32.5)	1.21	(1.07–1.37)	0.002
Q4 (155 ≤ CPG, mg/dL), n = 2,569	1,034 (40.3)	1.60	(1.42–1.81)	<0.001
<i>p</i> For trend				<0.001
Per 1 SD		1.16	(1.11–1.20)	<0.001
Glycemic control				
G1 (HbA1c < 6.0, %), n = 5,502	1,698 (30.9)	1.00	(Reference)	
G2 (6.0 ≤ HbA1c < 7.0, %), n = 2,781	879 (31.6)	1.04	(0.94–1.15)	0.46
G3 (7.0 ≤ HbA1c < 8.0, %), n = 975	378 (38.8)	1.34	(1.15–1.54)	<0.001
G4 (8.0 ≤ HbA1c, %), n = 925	406 (43.9)	1.51	(1.30–1.75)	<0.001
<i>p</i> For trend				<0.001
Per 1 SD		1.12	(1.08–1.17)	<0.001
Insulin resistance				
Q1 (HOMA-IR <1.03), n = 2,105	636 (30.2)	1.00	(Reference)	
Q2 (1.03 ≤HOMA-IR <1.70), n = 2,136	751 (35.2)	1.14	(1.00–1.30)	0.05
Q3 (1.70 ≤HOMA-IR <2.98), n = 2,137	716 (33.5)	1.01	(0.88–1.15)	0.94
Q4 (2.98 ≤ HOMA-IR), n = 2,125	730 (34.4)	1.06	(0.92–1.21)	0.44
<i>p</i> For trend				0.91
Per 1 log SD		1.02	(0.97–1.07)	0.43

Abbreviations: PCIS = posterior circulation ischemic stroke, OR = odds ratio, FPG = fasting plasma glucose, CPG = casual plasma glucose, HbA1c = hemoglobin A1c, HOMA-IR = homeostasis model assessment insulin resistance.

Q1–Q4 indicate the quartile for each variable. HbA1c (%) was categorized into 4 groups (G1–G4) according to the criteria of the Japan Diabetes Society. The multivariable model included age, sex, hypertension, dyslipidemia, atrial fibrillation, smoking, drinking, body mass index, chronic kidney disease, coronary artery disease, previous stroke, and stroke subtype.

Similarly, FPG, CPG, and HbA1c were associated with PCIS, whereas HOMA-IR showed no significant association with PCIS.

To reduce the imbalance of covariates between the 2 groups, we then investigated the associations after matching or weighting by the propensity score. In the propensity score-

matched cohort, background characteristics were not significantly different between the groups (table e-3, links.lww.com/CPJ/A80). Nonetheless, similar associations were still found between diabetes, FPG, CPG, and HbA1c, and PCIS (table 3). In addition, we estimated average treatment effects

of diabetes and glycemic parameters on PCIS by inverse probability weighting by the propensity scores (table e-4). We found that the estimated average treatment effect on PCIS significantly increased with diabetes, FPG, CPG, and HbA1c, but not with HOMA-IR.

Table 3 Associations between diabetes or glycemic parameters and PCIS in a propensity score-matched cohort

	PCIS (%)	OR	(95% CI)	p Value
Diabetes				
Nondiabetes, n = 3,129	947 (30.3)	1.00	(Reference)	
Diabetes, n = 3,129	1,199 (38.3)	1.41	(1.25–1.60)	<0.001
FPG				
Q1 (FPG <96, mg/dL), n = 1,415	454 (32.1)	1.00	(Reference)	
Q2 (96 ≤ FPG <111, mg/dL), n = 1,306	433 (33.2)	1.05	(0.81–1.35)	0.72
Q3 (111 ≤ FPG <138, mg/dL), n = 1,303	449 (34.5)	1.27	(0.99–1.62)	0.06
Q4 (138 ≤ FPG, mg/dL), n = 1,332	514 (38.6)	1.72	(1.35–2.20)	<0.001
p For trend				<0.001
Per 1 SD		1.18	(1.09–1.28)	<0.001
CPG				
Q1 (CPG <108, mg/dL), n = 1,628	506 (31.1)	1.00	(Reference)	
Q2 (108 ≤ CPG <130, mg/dL), n = 1,493	432 (28.9)	0.92	(0.73–1.15)	0.46
Q3 (130 ≤ CPG <175, mg/dL), n = 1,573	546 (34.7)	1.22	(0.98–1.51)	0.07
Q4 (175 ≤ CPG, mg/dL), n = 1,543	657 (42.6)	1.89	(1.53–2.33)	<0.001
p For trend				<0.001
Per 1 SD		1.23	(1.15–1.31)	<0.001
Glycemic control				
Q1 (HbA1c < 6.0, %), n = 2,517	780 (31.0)	1.00	(Reference)	
Q2 (6.0 ≤ HbA1c < 7.0, %), n = 1,904	614 (32.3)	1.07	(0.90–1.28)	0.44
Q3 (7.0 ≤ HbA1c < 8.0, %), n = 923	359 (38.9)	1.53	(1.23–1.91)	<0.001
Q4 (8.0 ≤ HbA1c, %), n = 878	382 (43.5)	1.74	(1.39–2.18)	<0.001
p For trend				<0.001
Per 1 SD		1.18	(1.11–1.26)	<0.001
Insulin resistance				
Q1 (HOMA-IR <1.13), n = 1,314	408 (31.1)	1.00	(Reference)	
Q2 (1.13 ≤ HOMA-IR <1.88), n = 1,292	468 (36.2)	1.13	(0.86–1.48)	0.38
Q3 (1.88 ≤ HOMA-IR <3.32), n = 1,288	456 (35.4)	1.14	(0.87–1.49)	0.34
Q4 (3.32 ≤ HOMA-IR), n = 1,295	462 (35.7)	1.29	(0.97–1.71)	0.08
p For trend				0.09
Per 1 log SD		1.09	(0.99–1.20)	0.09

Abbreviations: PCIS = posterior circulation ischemic stroke, OR = odds ratio, FPG = fasting plasma glucose, CPG = casual plasma glucose, HbA1c = hemoglobin A1c, HOMA-IR = homeostasis model assessment insulin resistance. Q1–Q4 indicate the quartile for each variable. HbA1c (%) was categorized into 4 groups (G1–G4) according to the criteria of the Japan Diabetes Society.

Associations between diabetes or glucose metabolism and PCIS in patients with thrombotic stroke

We further investigated the associations in patients with ischemic stroke because of thrombotic occlusion. In patients with thrombotic stroke, diabetes, FPG, CPG, and HbA1c were associated with PCIS, whereas there was no significant association between HOMA-IR and PCIS (table 4). Even in the propensity score-matched cohort, the associations between diabetes, FPG, CPG, and HbA1c, and PCIS were maintained (table e-5, links.lww.com/CPJ/A80). These associations were also found after inverse probability weighting using the propensity score (table e-6).

Associations between glucose metabolism and PCIS in patients with diabetes

The calculated E values for the observed ORs (lower limit of the 95% CI) of PCIS for diabetes were 1.62 (1.48) in all patients and 1.85 (1.67) in patients with thrombotic stroke. To eliminate factors other than diabetes, we then evaluated patients who had been diagnosed with diabetes mellitus. In these diabetic patients, HbA1c was associated with PCIS, but HOMA-IR did not show a significant association with PCIS (table e-7, links.lww.com/CPJ/A80). Compared with diabetic patients who did not have microvascular complications, the OR of PCIS significantly increased in those with retinopathy, neuropathy, or nephropathy (table e-8). The significantly increased OR of PCIS was found in patients with thrombotic stroke.

Discussion

The main findings of this study were as follows: (1) diabetes mellitus was associated with PCIS; (2) glucose concentrations and HbA1c, but not HOMA-IR, were associated with PCIS; (3) these associations were maintained even after 1:1 nearest neighbor matching or inverse probability weighting by the propensity score; (4) associations between diabetes, glucose concentrations, and HbA1c with PCIS were present in patients with thrombotic stroke; and (5) the OR of PCIS increased for HbA1c and microvascular complications in diabetic patients. Our findings suggest that poor glycemic control contributes to a greater risk of thrombotic infarction in the posterior circulation of the brain.

Previous studies have suggested that brainstem infarctions are more common in diabetic than in nondiabetic patients.^{6-12,24} The Registry of the Canadian Stroke Network showed that diabetes is associated with PCIS, and that age, female sex, and atrial fibrillation are inversely associated with PCIS.⁹ The present study shows that diabetes is associated with a higher risk of PCIS of the thrombotic type, independent of other factors. This suggests that thrombotic occlusion may develop more frequently in the posterior circulation arteries than in the anterior circulation arteries in diabetic patients.

Our findings suggest that poor glycemic control contributes to a greater risk of thrombotic infarction in the posterior circulation of the brain.

In the present study, poor glycemic control was associated with PCIS. Furthermore, the OR of PCIS increased in diabetic patients with microvascular complications compared with those without complications. In diabetic patients, the risk of such complications is reduced by strict glycemic control, and therefore, poor glycemic control is thought to be involved in their development.²⁵⁻³¹ Similarly, the severity and/or duration of hyperglycemia may play an important role in the development of PCIS. Further study is required to elucidate the nature of the relationship between glycemic control and the risk of PCIS.

There are anatomical and functional differences between the anterior and posterior circulations. Anatomically, hypoplasia or aplasia is common in the vertebral artery, and 1 of the 2 arteries is mostly hypoplastic or ends at the posterior inferior cerebral artery. Thinner hypoplastic arteries may be more liable to thrombotic occlusion secondary to poor glycemic control.³ Furthermore, posterior circulation brain arteries have greater concentric intimal thickening, more elastin loss, and a greater proportion of the internal elastic lamina than do anterior circulation arteries.¹⁴ These histopathologic differences may contribute to the vulnerability of the posterior circulation to hyperglycemia. Functionally, an autoregulatory response may be less efficient in the posterior circulation than in the anterior circulation.¹³ The posterior circulation has less sympathetic innervation than the anterior circulation.³² Diabetic neuropathy may cause sympathetic denervation and thereby change the vascular tone of vertebro-basilar arteries. Thus, the posterior circulation may be more susceptible to injury due to impaired vascular tone than the anterior circulation in diabetic patients. Indeed, a previous study showed that diabetes causes discrepant remodeling between the anterior and posterior circulation by a mechanism involving glycated hemoglobin.³³ These mechanisms may account for the increased risk of PCIS due to thrombotic occlusion after exposure to chronic hyperglycemia.

The present study has several limitations. Whether the association between diabetes and PCIS is because of unmeasured confounding still needs to be determined. Glycemic parameters were measured after the onset of stroke and therefore may not reflect actual glycemic status before stroke. There were missing values in the data sets of the glycemic parameters, including FPG (14.4%), CPG (0.4%), HbA1c (0.6%), fasting IRI (16.4%), and HOMA-IR (17.0%), which might lead to selection bias. Our

Table 4 Associations between diabetes or glycemic parameters and PCIS in patients with thrombotic stroke

	PCIS (%)	Multivariable-adjusted		
		OR	(95% CI)	<i>p</i> Value
Diabetes				
No diabetes, n = 3,032	925 (30.5)	1.00	(Reference)	
Diabetes, n = 1,869	787 (42.1)	1.61	(1.42–1.82)	<0.001
FPG				
Q1 (FPG <95, mg/dL), n = 1,117	364 (32.6)	1.00	(Reference)	
Q2 (95 ≤ FPG <107, mg/dL), n = 943	319 (33.8)	1.02	(0.85–1.23)	0.81
Q3 (107 ≤ FPG <131, mg/dL), n = 1,039	364 (35.0)	1.06	(0.88–1.27)	0.54
Q4 (131 ≤ FPG, mg/dL), n = 1,015	422 (41.6)	1.37	(1.14–1.64)	0.001
<i>p</i> For trend				0.001
Per 1 SD		1.15	(1.08–1.22)	<0.001
CPG				
Q1 (CPG <105, mg/dL), n = 1,284	393 (30.6)	1.00	(Reference)	
Q2 (105 ≤ CPG <122, mg/dL), n = 1,167	360 (30.9)	0.99	(0.83–1.17)	0.88
Q3 (122 ≤ CPG <162, mg/dL), n = 1,211	418 (34.5)	1.16	(0.98–1.38)	0.08
Q4 (162 ≤ CPG, mg/dL), n = 1,216	535 (44.0)	1.68	(1.42–1.98)	<0.001
<i>p</i> For trend				<0.001
Per 1 SD		1.19	(1.12–1.25)	<0.001
Glycemic control				
G1 (HbA1c < 6.0, %), n = 2,376	744 (31.3)	1.00	(Reference)	
G2 (6.0 ≤ HbA1c < 7.0, %), n = 1,293	413 (31.9)	1.00	(0.86–1.16)	0.99
G3 (7.0 ≤ HbA1c < 8.0, %), n = 585	266 (45.5)	1.77	(1.46–2.13)	<0.001
G4 (8.0 ≤ HbA1c, %), n = 619	283 (45.7)	1.71	(1.42–2.05)	<0.001
<i>p</i> For trend				<0.001
Per 1 SD		1.19	(1.13–1.25)	<0.001
Insulin resistance				
Q1 (HOMA-IR <1.11), n = 994	333 (33.5)	1.00	(Reference)	
Q2 (1.11 ≤ HOMA-IR <1.82), n = 996	364 (36.6)	1.11	(0.92–1.34)	0.27
Q3 (1.82 ≤ HOMA-IR <3.16), n = 992	342 (34.5)	0.95	(0.78–1.15)	0.58
Q4 (3.16 ≤ HOMA-IR), n = 988	388 (39.3)	1.15	(0.95–1.40)	0.15
<i>p</i> For trend				0.38
Per 1 log SD		1.06	(0.99–1.14)	0.10

Abbreviations: PCIS = posterior circulation ischemic stroke, OR = odds ratio, FPG = fasting plasma glucose, CPG = casual plasma glucose, HbA1c = hemoglobin A1c, HOMA-IR = homeostasis model assessment insulin resistance.

Q1–Q4 indicate quartile of each variable. HbA1c (%) was categorized into 4 groups (G1–G4) according to the criteria by the Japan Diabetes Society. The multivariable model included age, sex, hypertension, dyslipidemia, atrial fibrillation, smoking, drinking, body mass index, chronic kidney disease, coronary artery disease, and previous stroke.

study enrolled Japanese patients, and further studies are required to confirm the relationship between glucose metabolism and PCIS in other populations.

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TAKE-HOME POINTS

- The posterior circulation is more susceptible to ischemia than the anterior circulation in patients with diabetes mellitus.
- Poor glycemic control may contribute to the increased risk of PCIS.
- More attention is required for PCIS as a potential complication of poorly controlled diabetes.

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Disclosure

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Appendix 1 Author contributions

Name	Location	Role	Contribution
Junya Kuroda, MD, PhD	Kyushu University, Japan	Author	Design and conceptualized study; analyzed the data; interpreted the data; drafted and revised the manuscript for intellectual content
Ryu Matsuo, MD, PhD	Kyushu University, Japan	Author	Major role in the acquisition of data; analyzed the data; interpreted the data; revised the manuscript for intellectual content
Yuko Yamaguchi, MPH	Kyushu University, Japan	Author	Analyzed the data; interpreted the data; revised the manuscript for intellectual content
Noriko Satoh, MD	Kyushu University, Japan	Author	Major role in the acquisition of data; analyzed the data; interpreted the data

Appendix 1 (continued)

Name	Location	Role	Contribution
Masahiro Kamouchi, MD, PhD	Kyushu University, Japan	Author	Design and conceptualized study; interpreted the data; drafted and revised the manuscript for intellectual content
Jun Hata, MD, PhD	Kyushu University, Japan	Author	Design and conceptualized study; interpreted the data; revised the manuscript for intellectual content
Yoshinobu Wakisaka, MD, PhD	Kyushu University, Japan	Author	Interpreted the data; revised the manuscript for intellectual content
Tetsuro ago, MD, PhD	Kyushu University, Japan	Author	Interpreted the data; revised the manuscript for intellectual content
Takanari Kitazono, MD, PhD	Kyushu University, Japan	Author	Design and conceptualized study; interpreted the data; revised the manuscript for intellectual content

Appendix 2 Co-investigators

Name	Location	Role	Contribution
Setsuro Ibayashi, MD, PhD	Seiai Rehabilitation Hospital, Japan	Chair, Steering Committee	Led and coordinated communication among sites; critically reviewed the study proposal
Yasushi Okada, MD, PhD	Kyushu Medical Center, Japan	Vice-Chair, Site PI, Steering Committee	Led and coordinated communication among sites; critically reviewed the study proposal; collected data
Tetsuhiko Nagao, MD, PhD	Seiai Rehabilitation Hospital, Japan	Safety Monitoring Committee	Served as scientific advisor; monitored patient safety, critically reviewed the study protocol
Takao Ishitsuka, MD, PhD	Fukuoka Mirai Hospital, Japan	Steering Committee	Served as scientific advisor; critically reviewed the study proposal
Kenji Kusuda, MD, PhD	Seiai Rehabilitation hospital, Japan	Steering Committee	Served as scientific advisor; critically reviewed the study proposal
Kenichiro Fujii, MD, PhD	Moji Ekisaikai Hospital, Japan	Steering Committee	Served as scientific advisor; critically reviewed the study proposal; collected data
Masahiro Yasaka, MD, PhD	Kyushu Medical Center, Japan	Site Investigator, Steering Committee	Served as scientific advisor; critically reviewed the study proposal; collected data; provided and cared for study patients

Continued

Appendix 2 (continued)

Name	Location	Role	Contribution
Hiroaki Ooboshi, MD, PhD	Fukuoka Dental College, Japan	Steering Committee	Served as scientific advisor; critically reviewed the study proposal
Katsumi Irie, MD, PhD	Hakujuji Hospital, Japan	Steering Committee	Served as scientific advisor; critically reviewed the study proposal
Tsuyoshi Omae, MD, PhD	Imazu Red Cross hospital, Japan	Steering Committee	Served as scientific advisor; critically reviewed the study proposal
Kazunori Toyoda, MD, PhD	National Cerebral and Cardiovascular Center, Japan	Steering Committee	Served as scientific advisor; critically reviewed the study proposal
Hiroshi Nakane, MD, PhD	Fukuoka-Higashi Medical Center, Japan	Site PI, Steering Committee	Served as scientific advisor; critically reviewed the study proposal; collected data; provided and cared for study patients
Hiroshi Sugimori, MD, PhD	Saga-Ken medical Centre Koseikan	Site Investigator, Steering Committee	Served as scientific advisor; critically reviewed the study proposal; collected data; provided and cared for study patients
Shuji Arakawa, MD, PhD	Steel Memorial Yawata Hospital, Japan	Site PI, Steering Committee	Served as scientific advisor; critically reviewed the study proposal; collected data; provided and cared for study patients
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Shigeru Fujimoto, MD, PhD	Jichi Medical University, Japan	Steering Committee	Served as scientific advisor; critically reviewed the study proposal; collected data; provided and cared for study patients
Shoji Arihiro, MD	Kyushu Rosai hospital, Japan	Site PI, Steering Committee	Served as scientific advisor; critically reviewed the study proposal; collected data; provided and cared for study patients

Appendix 2 (continued)

Name	Location	Role	Contribution
Yoshihisa Fukushima, MD	St. Mary's Hospital, Japan	Site Investigator, Steering Committee	Served as scientific advisor; critically reviewed the study proposal; collected data; provided and cared for study patients

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