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ORIGINAL ARTICLE
Epidemiology

Nonfasting Glucose and Incident Stroke and Its Types
— The Circulatory Risk in Communities Study (CIRCS) —

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Background: The effect of postprandial glucose on the risk of cardiovascular disease has been emphasized, but it is controversial whether nonfasting glucose is related to incident stroke and its types.

Methods and Results: We investigated the associations of nonfasting glucose with incident stroke and its types among 7,198 participants aged 40–74 years from the Circulatory Risk in Communities Study, enrolled in 1995–2000. We estimated multivariable hazard ratios (HR) using Cox proportional hazard models. Over a median follow-up of 14.1 years, 291 cases of total stroke (ischemic strokes: 191 including 109 lacunar infarctions) were identified. Nonfasting glucose concentration was associated with greater risk of incident total stroke, ischemic stroke and lacunar infarction when modeled categorically (for prediabetic type: 7.8–11.0 mmol/L vs. normal type: <7.8 mmol/L among all subjects, HR for lacunar infarction was 2.02, 95% confidence interval (CI): 1.19, 3.43) or continuously (per one standard deviation increment among all subjects, HR for lacunar infarction was 1.29, 95% CI: 1.15, 1.45). Diabetic type showed similar results. Population attributable fractions of nonfasting hyperglycemia were 13.2% for ischemic stroke and 17.4% for lacunar infarction.

Conclusions: Nonfasting glucose concentration, either as a diagnosis of prediabetic and diabetic types or as a continuous variable, proved to be an independent predictor significantly attributed to incident total stroke, especially ischemic stroke and lacunar infarction, in the general population.

Key Words: Ischemic stroke; Lacunar infarction; Nonfasting glucose; Population-based cohort study; Prediabetic type

Patients with diabetes mellitus have a 2-fold higher risk of total stroke,[1] a 2.3-fold higher risk for ischemic stroke, and a 1.6-fold higher risk for hemorrhagic stroke,[2] while patients with prediabetes have a 1.3-fold higher risk of total stroke.[3] Furthermore, the glucose concentration 1–2 h after a meal was a stronger predictor for cardiovascular events than the fasting glucose concentration in cohort studies of patients with type 2 diabetes.[4,5] Usually, the increase in the postprandial blood glucose level precedes the increase in fasting blood glucose (FBG) level.[6] These findings support the importance of managing postprandial or post-load glucose for preventing cardiovascular disease (CVD).[6,7] However, less is known about the association of postprandial glucose with the risk of stroke or its types, compared with CVD or coronary artery disease (CAD). Specifically, no studies have yet focused on the association of postprandial prediabetic glucose levels with the risk of lacunar infarction, which is a more common type of ischemic stroke among non-Whites,[8,9] and the most common type of ischemic stroke in Japan.[10] Even in Western countries with aging populations there is

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concern over the possibility of increased rates of lacunar infarction because the risk of lacunar infarction increases with age.[11]

The 1–2 h post-load or postprandial glucose levels are difficult to obtain at health screenings for the general population because of time constraints. Therefore, the nonfasting (i.e., after natural individual meal times) glucose concentration is used in such situations. We previously reported that nonfasting glucose levels, either as a diagnosis of diabetic classification or as a continuous variable, proved to be an independent predictor for the incidence of CAD and myocardial infarction in a population-based cohort study.[12] Several previous cohort studies also reported an association between nonfasting glucose levels and the risk of stroke,[13,14] but a significant association was detected only for diabetes after multivariable adjustment.

In the present study, we investigated whether the nonfasting glucose level was associated with the risk of stroke and its types, including lacunar infarction, among Japanese men and women living in 4 different communities.

Methods

Study Populations

The study populations comprised 10,816 residents (4,097 men, 6,719 women) aged 40–74 years in the 1995–2000 baseline surveys of the Circulatory Risk in Communities Study (CIRCS), which is an ongoing dynamic community cohort study since 1963.[15,16] To avoid potential selection bias and recall bias, we used a prospective cohort study design. The participants were from 4 communities: Ikawa town[17,18] (a rural community in the Akita Prefecture of northwestern Japan), the Minami-Takayasu district[17] in Yao City (a southwestern suburb in the Osaka Prefecture), Noichi town[19] (a rural community in the Kochi Prefecture of southwestern Japan), and Kyowa town[20] (a rural community in Ibaraki Prefecture in central Japan). The census population aged 40–74 years in 1995 was 3,079 for Ikawa town, 10,123 for the Minami-Takayasu district, 6,981 for Noichi town, and 7,719 for Kyowa town. The study participation rate was 39%. Selection bias and recall bias were low. A total of 7,367 participants had data for their nonfasting glucose levels (i.e., time interval between testing and last meal <8 h). After exclusion of the participants with a history of stroke or CAD at baseline, the data for 7,198 subjects (2,567 men, 4,631 women) were included in the analyses.

Informed consent was obtained for conducting this study, based on the guidelines of the Council for International Organizations of Medical Science.[21] This study was approved by the ethics committees of the Osaka Medical Center for Health Science and Promotion and of Osaka University.

Follow-up and Ascertainment of Cases

Follow-up lasted until the end of 2010 in Noichi, 2011 in Kyowa and 2013 in both Ikawa and Minami-Takayasu. Follow-up was also terminated at the first incident of stroke, moving away from the community, or death.

As the details of endpoint determination have been described in previous CIRCS reports,[15,18] the ascertainment system for CVD in CIRCS has used the same diagnostic criteria throughout all study periods. Stroke endpoints were ascertained from death certificates, national insurance claims, annual questionnaires, annual cardiovascular risk surveys, and reports by local physicians, public health nurses, or health volunteers. To confirm the diagnosis, all living patients were telephoned, visited, or invited to take part in risk factor surveys, or alternatively, a medical history was obtained from their families. In addition, medical records from the local clinics and hospitals were reviewed. In the case of death, histories were obtained from families and/or attending physicians and medical records were reviewed. Stroke was defined as a focal neurological disorder with rapid onset and persisting for at least 24 h or until death. The determination of stroke subtype (intraparenchymal hemorrhage, subarachnoid hemorrhage, lacunar infarction, large-artery embolism, large-artery thrombosis, unclassified large-artery infarction, unclassified infarction, and unclassified stroke) was performed from the CT/MRI findings according to our previous report.[22] The CT/MRI findings were available for 92% of the stroke cases. Strokes that were diagnosed clinically but showed no lesion on CT/MRI were classified according to the clinical criteria. Final diagnoses were determined by a panel of 3–4 physicians participating in this study who were blinded to the data from the risk factor survey.

Baseline Examination

Blood was drawn into a serum separating tube and the serum was separated immediately after centrifugation and stored at −80°C for analysis. The time intervals since the last meal were 0 to <1 h (3.7%), 1 to <2 h (27.0%), 2 to <3 h (29.0%), 3 to <4 h (17.2%), and 4 to <8 h (23.2%). Serum glucose was determined by the glucokinase method using an Autoanalyzer 7250 (Hitachi Medical Corp., Ibaraki, Japan). Glucose values were subsequently divided into 3 categories (normal, prediabetic type, diabetic type). Here, normal was defined as no use of medication for diabetes mellitus and a nonfasting glucose level <7.8 mmol/L. Prediabetic type was defined by no use of medication for diabetes mellitus and a nonfasting glucose level of 7.8–11.0 mmol/L. Diabetic type was defined as having a nonfasting glucose level ≥11.1 mmol/L, or the use of medication for diabetes mellitus.

Total serum cholesterol was determined by an enzymatic assay, serum triglycerides were determined by an enzymatic assay for free glycerol, and serum high-density lipoprotein (HDL) levels were determined by a dextran sulfate-phosphotungstate-$MgCl_2$ precipitation method using an Autoanalyzer 7250 (Hitachi Medical Corp.). All measurements were performed at the laboratory of the Osaka Medical Center for Health Science and Promotion, an international member of the US National Cholesterol Reference Method Laboratory Network. The laboratory tests have been standardized since 1975 by the Centers for Disease Control-National Heart Lung and Blood Institute (CDC-NHLBI) Lipid Standardized Program provided by the CDC (Atlanta, GA, USA) and successfully met the criteria for both precision and accuracy of cholesterol measurements.[23–25]

Blood pressure (BP) was measured by trained physicians using standard mercury sphygmomanometers and unified epidemiological methods.[15] Hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg and/or antihypertensive medication use. Height was measured with the subjects in stocking feet and weight while wearing light clothing. The body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). We diagnosed atrial fibrillation (AF) from standard 12-lead ECG.

Table 1. Age-Adjusted Mean Values (Standard Errors) or Prevalence of Risk Characteristics at Baseline According to the Serum Glucose Category for Total Subjects

	Men				Women			
	Normal type	Prediabetic type	Diabetic type	P value for difference	Normal type	Prediabetic type	Diabetic type	P value for difference
No. at risk	2,072	317	178		4,171	279	181	
Age, years	58.9 (0.2)	60.9 (0.5)	62.2 (0.7)	<0.001	57.4 (0.1)	61.9 (0.6)	62.2 (0.7)	<0.001
Serum glucose, mmol/L	5.7 (0.0)	8.9 (0.1)	13.3 (0.1)	<0.001	5.5 (0.0)	8.7 (0.1)	11.9 (0.1)	<0.001
Body mass index, kg/m^2	23.4 (0.1)	23.8 (0.2)	24.0 (0.2)	0.008	23.4 (0.1)	24.3 (0.2)	24.7 (0.2)	<0.001
Systolic BP, mmHg	138 (0.4)	141 (1.1)	144 (1.5)	<0.001	135 (0.3)	138 (1.2)	140 (1.4)	<0.001
Diastolic BP, mmHg	83 (0.3)	82 (0.7)	81 (0.9)	0.014	79 (0.2)	79 (0.7)	79 (0.8)	0.548
Antihypertensive medication use, %	17.5	22.0	31.3	<0.001	16.3	21.3	39.4	<0.001
Hypertension, %	53.9	61.7	66.0	<0.001	44.8	54.7	59.7	<0.001
Atrial fibrillation, %	1.1	1.4	3.1	0.060	0.3	0.6	0.4	0.853
Serum total cholesterol, mmol/L	5.12 (0.02)	5.03 (0.05)	5.09 (0.07)	0.232	5.50 (0.01)	5.45 (0.06)	5.60 (0.07)	0.208
Serum triglycerides, mmol/L	1.69 (0.02)	1.82 (0.06)	2.13 (0.08)	<0.001	1.43 (0.01)	1.68 (0.05)	1.60 (0.07)	<0.001
Serum HDL-cholesterol, mmol/L	1.38 (0.01)	1.36 (0.02)	1.30 (0.03)	0.036	1.51 (0.01)	1.48 (0.02)	1.48 (0.03)	0.117
Current smoker, %	49.3	50.8	50.7	0.835	5.5	5.6	8.8	0.174
Ex-smoker, %	14.0	15.3	12.7	0.702	3.7	4.6	5.6	0.359
Ethanol intake, g/day	23.4 (0.5)	24.5 (1.3)	23.4 (1.7)	0.734	1.5 (0.1)	1.3 (0.3)	1.0 (0.4)	0.545
Postmenopausal, %					74.1	73.0	72.6	0.701

In parentheses: standard errors. BP, blood pressure; HDL-cholesterol, high-density lipoprotein-cholesterol.

During baseline surveys, we interviewed subjects to determine their medical history, smoking status, number of cigarettes per day, usual alcohol intake per week, and medication use for hypertension and diabetes.

Statistical Analysis

Analysis of covariance was used to test for differences in age-adjusted means and proportions of baseline characteristics according to overall serum glucose category. Hazard ratios (HRs) and 95% confidence intervals (CIs) for incidents of stroke and its types were calculated with the aid of Cox proportional hazards regression models. We tested the assumption of proportional hazards and found no violation of the proportionality principle.

We calculated the sex-specific and sex-adjusted HRs of the prediabetic and diabetic types against the normal serum glucose subgroup as a reference, and the corresponding HRs per 1 standard deviation increment in serum glucose level (2.2 mmol/L). The initial model was adjusted only for age, while the multivariable adjustment included adjustments for age, sex (for total participants), community, systolic BP, antihypertensive medication use, sex-specific quartiles of BMI (kg/m^2), AF, serum triglycerides (mmol/L), sex-specific quartiles of serum HDL-cholesterol (mmol/L), and the time interval since the last meal. The only missing data was for BMI, BP and HDL-cholesterol and the rate of missing data for BMI and BP was <0.1%, and for HDL-cholesterol it was 2.1%. We used dummy variables for missing data.

Specific population attributable fractions (PAFs) of nonfasting glucose categories for the risk of stroke and its types were calculated using the formula: PAF=Pe*(RR−1)/RR, where Pe is the exposure prevalence among cases and RR is the multivariable HR.[26] We also calculated approximate estimates of 95% CIs for the PAFs.[27]

All statistical analyses were performed with the Statistical Analysis System (SAS) for Windows (version 9.4; SAS Inc., Cary, NC, USA). All P-values for statistical tests were 2-tailed, and values <0.05 were regarded as statistically significant.

Results

Table 1 compares the age-adjusted mean values and prevalences of selected cardiovascular risk factors at baseline by serum glucose category. The prevalence of prediabetic type was 12.3% in men and 6.0% in women, and the corresponding prevalences of the diabetic type were 6.9% and 3.9%. Glucose abnormality was positively associated with age, BMI, systolic BP levels, antihypertensive medication, hypertension and serum triglycerides levels for both sexes, as well as with diastolic BP levels and AF in men. Glucose abnormality was inversely associated with serum HDL-cholesterol levels only in men. Smoking and drinking habits were not associated with the glucose category.

During the 14.1-year follow-up including 99,552 person-years, we documented 291 incidents of stroke (137 in men, 154 in women), 299 people who moved away from their baseline community (86 men, 213 women) and 1,085 deaths (614 men, 471 women). The observed strokes included 95 hemorrhagic strokes (58 intraparenchymal hemorrhages and 37 subarachnoid hemorrhages), 190 ischemic strokes

(109 lacunar infarctions, 26 large-artery embolisms, 17 large-artery thromboses, 9 unclassified large-artery infarctions and 29 unclassified infarctions), and 6 unclassified strokes.

Table 2 shows the association between serum glucose category and the risk for stroke and stroke types. The multivariable HRs of total stroke for prediabetic type vs. normal type were approximately 1.7 to 1.9, and were statistically significant in men and the total subjects. The corresponding HRs for ischemic stroke were 1.8 to 2.2, and were statistically significant in men, women, and the total subjects. Those for lacunar infarction were 1.9 to 2.1, and statistically significant for the total subjects. The multivariable HRs for total stroke for diabetic type vs. normal type were not significant. The corresponding HRs for ischemic stroke were 1.2 to 2.8, and were statistically significant in women and the total subjects. Those for lacunar infarction were 1.8 to 3.5, and were statistically significant in women and the total subjects. The multivariable HRs of total stroke for hyperglycemia (total of prediabetic and diabetic types) vs. normal type were approximately 1.5 and statistically significant for the total subjects. The corresponding HRs of ischemic stroke were 1.6 to 2.5 and statistically significant in men, women, and the total subjects. Those of lacunar infarction were 1.9 to 2.7 and statistically significant in men, women and the total subjects. The multivariable HRs of total stroke associated with 1 standard deviation (2.16 mmol/L) increment of serum glucose were 1.1 to 1.2, and statistically significant in women and the total subjects. The corresponding HRs of ischemic stroke were 1.1 to 1.3 and were statistically significant in women and the total subjects. Those of lacunar infarction were 1.2 to 1.3 and were significant in men, women, and the total subjects.

The PAFs of prediabetic type among the total subjects were 7.7% for total stroke, 8.5% for ischemic stroke and 8.8% for lacunar infarction and each PAF was statistically significant. The corresponding PAFs of diabetic type among the total subjects were 0.8%, 4.7% and 8.7%, and the PAF was statistically significant only for lacunar infarction. The corresponding PAFs of hyperglycemia among the total subjects were 8.6%, 13.2%, and 17.4% and each PAF was statistically significant. When analyzed by sex, the PAFs of hyperglycemia were statistically significant only for ischemic stroke (14.5%) and lacunar stroke (17.7%) in women.

When we excluded the subjects who took medication for diabetes mellitus (n=205, 57% of diabetic type), the results did not change substantially. For example, the multivariable HRs of lacunar infarction for hyperglycemia vs. normal

Table 2. Multivariable HRs (95% CI) of Total Stroke, Hemorrhagic Stroke, Ischemic Stroke and Lacunar Infarction According to the Serum Glucose Category and Glucose Concentration for Total Subjects

	Person-years	Total stroke				Hemorrhagic stroke			
		No. of events	Age-adjusted HR (95% CI)§	Multivariable HR (95% CI)	PAF	No. of events	Age-adjusted HR (95% CI)§	Multivariable HR (95% CI)	PAF
Men									
Normal type	27,828	95	Ref.	Ref.		25	Ref.	Ref.	
Prediabetic type	3,952	32	2.13 (1.42~3.18)‡	1.90 (1.24~2.90)†	11.1 (2.2~19.1)*	9	2.31 (1.08~4.96)*	2.03 (0.90~4.56)	13.4 (−6.4~29.5)
Diabetic type	2,104	10	1.20 (0.62~2.30)	0.86 (0.44~1.69)	−1.1 (−6.4~3.7)	0			
Hyperglycemia¶	6,056	42	1.80 (1.25~2.59)†	1.48 (1.01~2.19)*	9.9 (−1.1~19.8)	9	1.51 (0.70~3.24)	1.20 (0.53~2.70)	4.4 (−18.2~22.7)
HR per 1 SD increment of glucose	33,884	137	1.16 (1.03~1.30)*	1.08 (0.95~1.23)		34	1.05 (0.80~1.38)	0.93 (0.68~1.28)	
Women									
Normal type	59,629	125	Ref.	Ref.		54	Ref.	Ref.	
Prediabetic type	3,673	17	1.64 (0.99~2.74)	1.66 (0.98~2.82)	4.4 (−1.2~9.7)	6	1.51 (0.65~3.54)	1.24 (0.52~2.98)	1.9 (−6.8~9.9)
Diabetic type	2,367	12	1.86 (1.03~3.37)*	1.49 (0.80~2.77)	2.6 (2.1~7.0)	1	0.39 (0.05~2.83)	0.25 (0.03~1.84)	−4.9 (−10.1~0.1)
Hyperglycemia¶	6,040	29	1.73 (1.15~2.60)†	1.59 (1.04~2.43)*	7.0 (−0.5~14.0)	7	1.07 (0.49~2.37)	0.80 (0.35~1.80)	−2.9 (−13.2~6.5)
HR per 1 SD increment of glucose	65,669	154	1.24 (1.09~1.41)‡	1.19 (1.05~1.36)†		61	1.04 (0.78~1.37)	0.91 (0.66~1.24)	
Total									
Normal type	87,457	220	Ref.	Ref.		79	Ref.	Ref.	
Prediabetic type	7,625	49	1.94 (1.42~2.65)‡	1.84 (1.33~2.55)‡	7.7 (2.7~12.4)†	15	1.90 (1.08~3.33)*	1.64 (0.91~2.93)	6.2 (−2.6~14.2)
Diabetic type	4,471	22	1.48 (0.95~2.30)	1.12 (0.71~1.77)	0.8 (−2.6~4.1)	1	0.21 (0.03~1.53)	0.14 (0.02~1.01)	−6.4 (−8.2~−4.8)†
Hyperglycemia¶	12,095	71	1.77 (1.35~2.32)‡	1.54 (1.16~2.05)†	8.6 (2.2~14.5)†	16	1.27 (0.74~2.19)	0.99 (0.56~1.74)	−0.2 (−10.2~9.0)
HR per 1 SD increment of glucose	99,553	291	1.19 (1.10~1.30)‡	1.13 (1.03~1.24)†		95	1.04 (0.86~1.27)	0.93 (0.75~1.16)	

(**Table 2** continued the next page.)

	Ischemic stroke				Lacunar infarction			
	No. of events	Age-adjusted HR (95% CI)§	Multivariable HR (95% CI)	PAF	No. of Events	Age-adjusted HR (95% CI)§	Multivariable HR (95% CI)	PAF
Men								
Normal type	68	Ref.	Ref.		38	Ref.	Ref.	
Prediabetic type	22	2.03 (1.26~3.29)†	1.82 (1.09~3.02)*	9.9 (–0.3~19.1)	13	2.11 (1.12~3.97)*	1.88 (0.97~3.65)	1.03 (–3.1~22.0)
Diabetic type	10	1.64 (0.84~3.19)	1.21 (0.61~2.43)	1.7 (–5.2~8.2)	8	2.31 (1.07~4.95)*	1.83 (0.82~4.08)	6.2 (–4.1~15.4)
Hyperglycemia¶	32	1.89 (1.24~2.89)†	1.58 (1.00~2.48)*	11.7 (–1.5~23.3)	21	2.18 (1.28~3.72)†	1.86 (1.05~3.30)*	16.5 (–1.6~31.3)
HR per 1 SD increment of glucose	100	1.19 (1.05~1.36)†	1.13 (0.98~1.31)		59	1.26 (1.08~1.46)†	1.21 (1.02~1.43)*	
Women								
Normal type	68	Ref.	Ref.		36	Ref.	Ref.	
Prediabetic type	11	1.81 (0.95~3.43)	2.17 (1.12~4.24)*	6.6 (–1.0~13.6)	6	1.93 (0.81~4.59)	2.11 (0.86~5.15)	6.3 (–3.9~15.5)
Diabetic type	11	3.02 (1.59~5.71)‡	2.82 (1.43~5.57)†	7.9 (0.4~14.8)*	8	4.21 (1.95~9.08)‡	3.52 (1.55~7.98)†	11.5 (0.0~21.6)
Hyperglycemia¶	22	2.26 (1.40~3.67)‡	2.45 (1.47~4.10)‡	14.5 (3.6~24.1)*	14	2.80 (1.50~5.21)†	2.72 (1.41~5.22)†	17.7 (2.0~30.9)*
HR per 1 SD increment of glucose	90	1.34 (1.17~1.55)‡	1.34 (1.16~1.56)‡		50	1.46 (1.25~1.71)‡	1.40 (1.18~1.66)‡	
Total								
Normal type	136	Ref.	Ref.		74	Ref.	Ref.	
Prediabetic type	33	1.98 (1.35~2.91)‡	1.96 (1.31~2.94)†	8.5 (2.2~14.4)†	19	2.08 (1.25~3.47)†	2.02 (1.19~3.43)†	8.8 (0.4~16.5)*
Diabetic type	21	2.16 (1.36~3.43)†	1.74 (1.07~2.83)*	4.7 (–0.3~9.5)	16	3.01 (1.74~5.18)‡	2.45 (1.38~4.35)†	8.7 (1.2~15.6)*
Hyperglycemia¶	54	2.05 (1.49~2.82)‡	1.87 (1.33~2.63)‡	13.2 (4.8~20.9)†	35	2.43 (1.61~3.65)‡	2.19 (1.42~3.39)‡	17.4 (5.8~27.7)†
HR per 1 SD increment of glucose	190	1.25 (1.14~1.38)‡	1.22 (1.10~1.35)‡		109	1.34 (1.20~1.49)‡	1.29 (1.15~1.45)‡	

*P<0.05, †P<0.01, ‡P<0.001. §Adjusted for age and sex-adjusted HR for total subjects. ¶Hyperglycemia is combined prediabetic and diabetic. Multivariable hazard ratio adjusted for age, sex (for total subjects), systolic blood pressure, antihypertensive medication use, atrial fibrillation, serum triglycerides, sex-specific quartiles of body mass index, quartiles of serum high-density lipoprotein-cholesterol, time since the last meal and community. CI, confidence interval; HRs, hazard ratios; PAF, population attributable fraction; SD, standard deviation.

glucose levels were 1.74 (0.93–3.26) for men, 2.25 (1.01–4.99) in women and 1.92 (1.17–3.15) in the total subjects. The corresponding HRs of lacunar infarction associated with 1 standard deviation (1.86 mmol/L) increment of serum glucose were 1.17 (0.98–1.40) in men, 1.35 (1.10–1.65) in women and 1.24 (1.09–1.42) for the total subjects.

Discussion

The present community-based cohort study showed that the nonfasting glucose concentration, either as a diagnosis of prediabetic or diabetic classifications or as a continuous variable, was an independent predictor for incident total stroke, ischemic stroke, and lacunar infarction, especially in women.

The Funagata study of 2,938 Japanese men and women aged older than 35 years showed that persons with impaired glucose tolerance (IGT) by oral glucose tolerance test (OGTT) had 1.5-fold higher risk of total stroke than those with normal glucose tolerance.[28] However, the Hisayama study of 2,421 Japanese men and women aged 40–79 years showed that IGT by OGTT was not associated with risk of ischemic stroke or lacunar infarction.[29] A Japan Public Health Center-based prospective study (JPHC study) of 13,129 men and women aged 40–69 years using combined fasting and nonfasting glucose criteria showed that prediabetic women had a 1.8-fold higher risk of lacunar infarction, but prediabetic men had no associations with any type of stroke.[30] Our previous study (baseline data collected from 1975 to 1986) of 10,582 men and women aged 40–69 years, with a 17-year follow-up using combined fasting and nonfasting glucose criteria, indicated that the multivariable HRs of ischemic stroke and lacunar infarction for prediabetic participants were not significant in either men or women.[31] However, the present study showed that prediabetic participants had significantly higher risks of ischemic stroke and lacunar infarction. Some possible reasons for being able to detect the risk of ischemic stroke and lacunar stroke in the previous study were considered. First, the present study was limited to nonfasting subjects. Second, the rate of stroke confirmed by CT and/or MRI was higher (92% vs. 80%). Third, our previous study changed from the cupric-neocuproine method to the hexokinase method for measuring blood glucose during the baseline survey, but in the present study, we used a single method (glucokinase method).

Reasons for the weaker association of diabetic type with the risk of ischemic stroke than that of prediabetic type in men are uncertain. There is a possibility of competing risk

with CAD or cancer. However, the difference in risk of death from CAD between these 2 types was small: the multivariable HRs (95% CI)=2.43 (1.29–4.58) and 2.62 (1.46–4.67), respectively[32] and the difference in risk of total cancer between persons with and without a diabetes history was also small: the multivariable HRs (95% CI)=1.19 (1.12–1.15).[33] Thus, the effect of competing risk, if it exists, may be small. Another possible reason is more intensive medical control performed for diabetic type than for prediabetic type. In the present study, over half of the men with diabetic type (57%) were under medication for diabetes, and they were more likely to be treated for another major stroke risk factor (i.e., hypertension). The prevalence of antihypertensive medication use among hypertensives was 39.5% for prediabetic type and 57.8% for diabetic type, although the prevalence of hypertension was similar between the 2 types (62.4% and 68.0%, respectively).

What are the underlying mechanisms of the association between nonfasting glucose and the risk of stroke? First, insulin resistance (IR) maybe exist at the stage of prediabetic nonfasting glucose level, because IR is present at the stage of IGT.[34,35] IR promotes atherogenesis, inflammation, and leads to aggregation of other risk factors, such as dyslipidemia (high triglycerides, low HDL, and small dense low-density lipoprotein particles), hypertension, and endothelial dysfunction.[36] Second, the fluctuation in blood glucose level can lead to vascular complications through several mechanisms. The repetitive post-feeding fluctuations in glucose concentrations of diabetic rats caused monocytes to adhere to the endothelial cells of the thoracic aorta, even at mean hemoglobinA_{1c} (HbA_{1c}) levels <4.0%.[37] In rat models of diabetes induced by insulin-mediated rapid changes in blood glucose levels, endothelium-dependent relaxation is impaired.[38] Oxidative stress correlates with acute glucose fluctuations, but not with HbA_{1c} levels or fasting glucose concentrations.[39]

Lacunar infarction is a more common type of ischemic stroke among non-Whites,[8,9] especially among Japanese.[10] Moreover, in addition to Japan, Western countries with aging populations are concerned about the possibility of increased levels of lacunar infarction.[11] Its pathological characteristics differ substantially from those of atherosclerosis. Lacunar infarction is based on arteriosclerosis accompanied by fibrous cell proliferation for microaneurysm with loss of medial smooth-muscle cells, the infiltration of blood plasma into the intima, the histolysis of the internal elastic lamina and intimal collagen fibers, intimal fibrin deposition, and luminal dilatation.[10] In apolipoprotein E-deficient mice, repetitive post-feeding glucose spikes, induced by being fed maltose twice daily, accelerated the formation of fibrotic arteriosclerotic lesions.[40]

In our study, the HRs of ischemic stroke and lacunar infarction for participants classified as hyperglycemia (prediabetic and diabetic types) were greater in women than in men. The PAFs of hyperglycemia for ischemic stroke and lacunar infarction were statistically significant in women but not in men. A previous meta-analysis[1] showed the increased risk of stroke associated with diabetes is significantly higher in women than in men. An Italian prospective study of type 2 diabetic patients showed that blood glucose level at 2 h after lunch was a stronger predictor of cardiovascular events than FBG, particularly in women.[41] Another meta-analysis showed that the effect of hyperglycemia on the risk of CVD may be greater in women than in men.[42] The mechanism of the sex difference remains unclear. However, hyperglycemia may eliminate women's ability to protect against CVD risk through stronger additive or synergistic effects on smoking, hypertension, hypercholesterolemia, and being overweight compared with men.[43] Some sex hormones, such as bioavailable testosterone, can also contribute to the mechanism.[44]

Study Strengths and Limitations

First, we examined the associations of glucose category and of glucose concentration with risk of total stroke and its types, including lacunar infarction in men, women, and total subjects. Second, we used incidence as the target endpoint because it reflects more directly the relationship with glucose category or glucose concentration than does death from total stroke or its types. Third, our study was a community-based study and thus not limited to hyperglycemic patients, so our findings are likely to be generalizable. Fourth, we examined not only relative risk, but the PAFs of prediabetic and diabetic types for the risk of total stroke and its types.

The limitation of our study is that residual confounding cannot be ruled out, as for all observational studies. In addition, the population was limited to those aged 40–74 years and thus it is uncertain whether our findings are applicable to other age groups.

In conclusion, the nonfasting glucose concentration, either as a diagnosis of prediabetic and diabetic type or as a continuous variable, proved to be an independent predictor significantly attributed to incident total stroke, especially ischemic stroke and lacunar infarction, in a general population. Finally, nonfasting glucose measurements may be useful in predicting the risk of ischemic stroke and lacunar infarction.

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Disclosures

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