

## Original Article

# Risk of Cerebral Infarction assessed by Fasting Insulin and Fasting Glucose in a Japanese General Population : The Jichi Medical School Cohort Study

Yuji Kaneda<sup>1</sup>, Shizukiyo Ishikawa<sup>2</sup>, Tadao Goto<sup>3</sup>, Kazunori Kayaba<sup>4</sup>, Yoshikazu Yasuda<sup>1</sup>, Eiji Kajii<sup>2</sup>

<sup>1</sup>Department of Surgery, Jichi Medical University, Tochigi, Japan 329-0498

<sup>2</sup>Division of Community and Family Medicine, Center for Community Medicine, Jichi Medical University, Tochigi, Japan

<sup>3</sup>Wara National Health Insurance Clinic, Gujo, Gifu, Japan

<sup>4</sup>School of Health and Social Services, Saitama Prefectural University, Saitama, Japan

## Abstract

This study was performed to examine the relation between the risk of cerebral infarction and fasting insulin (FI) stratified by fasting glucose (FG) in a Japanese general population. The subjects were 2,608 men and women, examined between 1992 and 1995 as part of the Jichi Medical School Cohort Study. Subjects were divided into nine groups : group1 (G1) with tertile 1 (T1) of FI and T1 of FG, G2 with T2 of FI and T1 of FG, G3 with T3 of FI and T1 of FG, G4 with T1 of FI and T2 of FG, G5 with T2 of FI and T2 of FG, G6 with T3 of FI and T2 of FG, G7 with T1 of FI and T3 of FG, G8 with T2 of FI and T3 of FG and G9 with T3 of FI and T3 of FG. Cox's proportional hazard model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for cerebral infarction. During an average of 11.1 years of follow-up, 87 participants developed cerebral infarction. In multivariate-adjusted analysis, HRs of cerebral infarction were 3.93 (95% CI, 1.13 – 13.72) in G1, 2.30 (0.51 – 10.34) in G3, 2.19 (0.58 – 8.19) in G4, 1.18 (0.26 – 5.31) in G5, 2.96 (0.81 – 10.88) in G6, 3.48 (0.97 – 12.53) in G7, 2.39 (0.66 – 8.62) in G8 and 3.73 (1.09 – 12.84) in G9, using G2 as the reference. The association between FI and risk of cerebral infarction seemed to be U-shaped and this association was seen in each FG level.

(Key Words : Cerebral infarction, fasting insulin, fasting glucose, cohort study)

## Introduction

Insulin resistance (IR) is defined as a state of subnormal biologic response to a given concentration of insulin, and it has a key role in the pathogenesis of many disorders, including obesity and diabetes mellitus<sup>1</sup>. In addition, it is well established that IR is independently associated with risk of stroke<sup>2-7</sup>. To evaluate insulin resistance, several indices have been used, such as the homeostasis model assessment for insulin resistance (HOMA-IR)<sup>3-6</sup>. We reported that the relationship between IR measured by the HOMA-IR and cerebral infarction was not dose-dependent in a Japanese general population<sup>8</sup>. However, it is uncertain how CI events are influenced by fasting glucose (FG) and fasting insulin (FI), which are elements of HOMA-IR. The relation between FI and stroke was investigated in several prospective studies, but this relation is controversial and the

effect of FG is not taken into consideration<sup>6, 9, 10</sup>. In addition, little is known about the relationship between FI and the risk of cerebral infarction in a Japanese general population<sup>6</sup>. The aim of this study was to examine the relationship between risk of cerebral infarction and FI stratified by FG in a Japanese general population in a prospective study.

## Methods

### Subjects

The Jichi Medical School (JMS) Cohort Study was conducted to investigate the risk of cardiovascular disease in the Japanese population. Details of the JMS Cohort Study design and some descriptive data have been published previously<sup>11, 12</sup>. The baseline data of this cohort study were obtained between April 1992 and July 1995. In this study, participants were 12,490 Japanese men and

women who underwent mass screening programs in 12 communities across Japan. At least one JMS alumnus worked as a physician in each community. Mass screening for cardiovascular disease has been conducted in Japan since 1983 in accordance with the health and medical service law for the aged, and we used this system to collect the data for this study. In each community, a municipal government office sent personal invitations to all the potential participants for the examination by letter or using public information services. The overall participation rate was 65.4%.

The FI level was measured once at the baseline in three communities (Wara and Takasu in Gifu prefecture, Sakuma in Shizuoka prefecture) as an optional examination that included 3,100 subjects (1,338 men and 1,762 women). These three communities were rural areas like the other nine communities.

In this study, we excluded individuals who had a past history of stroke or myocardial infarction ( $n = 50$ ), who were undergoing treatment for diabetes mellitus ( $n = 61$ ), who were diagnosed as indeterminable cases in the diagnosis of stroke ( $n = 1$ ), whose data on blood samples could not be obtained ( $n = 28$ ), who did not respond to questions about past history of stroke, myocardial infarction, diabetes mellitus, hypertension, hyperlipidemia, alcohol consumption or smoking habit ( $n = 251$ ), and whose data regarding physical findings were incomplete ( $n = 101$ ). Finally, 2,608 subjects (1,095 men and 1,513 women) remained and were analyzed as study participants.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with a fully automated sphygmomanometer BP203RV-II (Nippon Colin, Komaki, Japan), placed on the right arm of the seated subject who had rested in the sitting position for five minutes before the measurement. Body mass index (BMI) was calculated as  $\text{weight (kg)}/\text{height (m)}^2$ . FG was measured by an enzymatic method (Kanto Chemistry, Tokyo, Japan; interassay CV: 1.9%). FI levels were determined with a radioimmunoassay kit (Dainabot, Tokyo, Japan; interassay CV: 4.5%). The lower detection limit was 2.5 mU/L, and insulin levels below this limit were taken as 2.0 mU/L. Triglycerides (TG) were measured by an enzymatic method (Wako, Osaka, Japan; interassay coefficient of variation (CV): 1.7%). High-density lipoprotein (HDL) cholesterol was measured using the phosphotungstate precipitation method (Wako, Osaka, Japan; interassay CV: 1.9%). Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula. The formula for LDL cholesterol was as follows:  $\text{LDL cholesterol (mg/dL)} = \text{Total cholesterol (mg/dL)} - \text{HDL cholesterol (mg/dL)} - \text{TG}/5 \text{ (mg/dL)}$ .

Information about medical history and lifestyle was obtained with a questionnaire. Smoking status was classified as current smoker or non-smoker. Drinking status was

classified as current drinker or non-drinker.

### Ethical Issues

Written informed consent for the study was obtained individually from all respondents of the mass screening. The study design and procedures were approved by each community government and the Ethical Committee of Epidemiologic Research at JMS.

### Follow-up System

We asked the subjects directly whether they had a history of stroke and/or cardiovascular diseases after enrolling in the present study by means of a health examination program in each community. If they had a history of such diseases, we asked which hospital they visited and when the disease was diagnosed. Subjects who did not come to the screening examination were contacted by mail or phone. We also checked the medical records to see if the subjects had been hospitalized. Public health nurses also visited the subjects to obtain additional information. If an incident was suspected, forms for stroke incidence were filled out and duplicate computer tomography films or magnetic resonance imaging films were obtained for diagnostic confirmation. We collected death certificates to ascertain the cause of death and date of death at the public health center of each community with permission from the Agency of General Affairs and the Ministry of Health, Labor, and Welfare. We were able to ascertain the endpoint of all participants who died between the date of their health examination and the end of 2002. Those who moved out of the communities during the observation period were followed until the date they left and data on these study subjects were obtained by each municipal government annually.

### Diagnostic Criteria

The diagnosis of stroke and stroke subtype were determined independently by the Diagnosis Committee. This included one radiologist, one neurologist and two cardiologists. Diagnosis of stroke was determined by the presence of a focal and nonconvulsive neurological deficit lasting for more than 24 hours with a clear onset. Stroke subtype was determined by the criteria of the National Institute of Neurological Disorder and Stroke.

### Statistical Analysis

Values are expressed as the mean  $\pm$  standard deviation (SD), except for TG, FG and FI. The distributions of TG, FG and FI were highly skewed; these data were expressed as the median and interquartile range and transformed into natural logarithms for statistical analysis. Data regarding proportions were expressed as a percentage. Categorical variables were compared using the chi-square test. Multiple group comparisons were evaluated by the Kruskal-Wallis

test. First, to investigate the risk of cerebral infarction associated with the FG and FI, we divided the participants into three groups according to the tertiles of FG and FI levels. Second, we defined the group with tertile 1 (T1) of FI and T1 of FG as group 1 (G1), with T2 of FI and T1 of FG as G2, with T3 of FI and T1 of FG as G3, with T1 of FI and T2 of FG as G4, with T2 of FI and T2 of FG as G5, with T3 of FI and T2 of FG as G6, with T1 of FI and T3 of FG as G7, with T2 of FI and T3 of FG as G8 and with T3 of FI and T3 of FG as G9. Cutoffs of tertiles for the FG were 88 and 96, for the FI were 3.2 and 5.4. Crude incidence rates of cerebral infarction were calculated per 1,000 person-years. We used Cox's proportional hazard model to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for cerebral infarction with FG tertiles, FI tertiles and 9 groups. HRs and 95% CIs were first calculated after adjustment for age and sex, and then for age, sex, SBP, HDL cholesterol, LDL cholesterol, TG, status of hypertension, hyperlipidemia, smoking status and drinking status. The tertile or group with the lowest risk of cerebral infarction was defined as the reference category. A significant difference was defined as  $p < 0.05$ . Statistical analyses were performed using SPSS version 20 (SPSS Inc, Japan).

## Results

During a mean follow-up of 11.1 years (Men, 10.9 years ; Women, 11.2 years), 87 of 2,608 participants experienced cerebral infarction (men, 46 cases ; women, 41 cases).

### Baseline Characteristics

Baseline characteristics of the study population in accordance with tertiles of the FG and FI at the baseline are shown in Table 1. FG levels were positively associated with age, BMI, SBP, DBP, TG and FI, inversely associated with HDL cholesterol. FI levels were positively associated with BMI, SBP, DBP, LDL cholesterol, TG and FG, inversely associated with age and HDL cholesterol.

### FG and Risk of Cerebral Infarction

Table 2 shows crude incidence rates and HRs for cerebral infarction by tertiles of FG. Crude incidence rates of FG tertiles 1-3 were 2.58, 2.35 and 4.06 per 1,000 person-years. The tertile with the lowest risk of cerebral infarction was T2. Therefore, we defined T2 as the reference category.

In age and sex-adjusted analysis (model 1), HRs were 1.16 (95% CI, 0.65 – 2.07) in T1 and 1.61 (95% CI, 0.96 – 2.68) in T3, using T2 as the reference. In multivariate-adjusted analysis (model 2), HRs for cerebral infarction were 1.23 (95% CI, 0.69 – 2.20) in T1 and 1.53 (95% CI, 0.91 – 2.56)

**Table 1. Baseline Characteristics of the Study Population**

	All	Fasting glucose, mg/dL			P value
		T 1 (< 88)	T 2 (88 – 95)	T 3 (96 ≤)	
Subjects	2608	795	886	927	
Age, years	57.3 ± 11.9	56.0 ± 12.5	56.9 ± 12.2	58.8 ± 10.8	< 0.001
Sex, men/women	1095/1513	295/500	339/547	461/466	< 0.001
Hypertension under treatment, %	11.5	10.1	11.1	13.3	0.100
Hyperlipidemia under treatment, %	2.3	2.3	2.1	2.6	0.811
Current smoking, %	22.5	26.7	19.8	21.5	< 0.005
Current alcohol drinking, %	49.9	50.3	48.5	50.8	0.599
Body mass index, kg/m <sup>2</sup>	22.8 ± 3.0	22.2 ± 2.7	22.7 ± 2.9	23.3 ± 3.2	< 0.001
Systolic blood pressure, mm Hg	130.2 ± 22.0	124.9 ± 21.6	129.2 ± 21.2	135.7 ± 21.9	< 0.001
Diastolic blood pressure, mm Hg	77.3 ± 12.7	74.2 ± 12.6	76.8 ± 12.1	80.4 ± 12.6	< 0.001
HDL cholesterol, mg/dL	49.8 ± 12.6	50.6 ± 13.4	50.0 ± 12.1	48.8 ± 12.4	< 0.010
LDL cholesterol, mg/dL	121.1 ± 31.3	119.1 ± 30.5	121.7 ± 30.9	122.1 ± 32.3	0.057
Triglycerides, mg/dL	89.0 (66.0 – 123.0)	80.0 (60.0 – 112.0)	88.0 (67.0 – 120.0)	96.0 (70.0 – 133.0)	< 0.001
Fasting insulin, mU/L	4.2 (2.7 – 6.3)	3.6 (2.0 – 5.4)	4.1 (2.6 – 6.1)	4.8 (3.1 – 7.5)	< 0.001
	All	Fasting Insulin, mU/L			P value
		T 1 (< 3.2)	T 2 (3.2 – 5.3)	T 3 (5.4 ≤)	
Subjects	2608	866	847	895	
Age, years	57.3 ± 11.9	58.7 ± 11.4	57.2 ± 12.1	56.0 ± 11.9	< 0.001
Sex, men/women	1095/1513	474/392	329/518	292/603	< 0.001
Hypertension under treatment, %	11.5	8.4	12.3	13.9	< 0.005
Hyperlipidemia under treatment, %	2.3	1.8	2.1	3.0	0.236
Current smoking, %	22.5	30.9	20.0	16.6	< 0.001
Current alcohol drinking, %	49.9	56.4	49.6	43.9	< 0.001
Body mass index, kg/m <sup>2</sup>	22.8 ± 3.0	21.4 ± 2.4	22.8 ± 2.6	24.1 ± 3.2	< 0.001
Systolic blood pressure, mm Hg	130.2 ± 22.0	125.8 ± 21.6	130.7 ± 22.0	133.9 ± 21.6	< 0.001
Diastolic blood pressure, mm Hg	77.3 ± 12.7	74.8 ± 12.0	77.6 ± 13.0	79.4 ± 12.6	< 0.001
HDL cholesterol, mg/dL	49.8 ± 12.6	53.3 ± 13.2	49.7 ± 12.1	46.4 ± 11.6	< 0.001
LDL cholesterol, mg/dL	121.1 ± 31.3	114.4 ± 30.1	123.8 ± 30.8	124.9 ± 32.0	< 0.001
Triglycerides, mg/dL	89.0 (66.0 – 123.0)	77.0 (59.0 – 105.0)	88.0 (65.0 – 120.0)	102.0 (78.0 – 142.0)	< 0.001
Fasting glucose, mg/dL	92.0 (86.0 – 99.0)	90.0 (85.0 – 96.0)	91.0 (86.0 – 98.0)	95.0 (88.0 – 102.0)	< 0.001

Values represent the mean ± SD or percent except for triglycerides, fasting glucose and fasting insulin, where median and interquartile ranges are shown.

T : tertile

**Table 2. Risk of Cerebral Infarction and Fasting Glucose Level**

	FG, mg/dL	Subjects	Cases	Crude Incidence Rates <sup>a</sup>	Model 1 <sup>b</sup>		Model 2 <sup>c</sup>	
					HR	95% CI	HR	95% CI
Tertile 1	< 88	795	23	2.58	1.16	0.65 – 2.07	1.23	0.69 – 2.20
Tertile 2	88 – 95	886	23	2.35	1.00	Reference	1.00	Reference
Tertile 3	96 ≤	927	41	4.06	1.61	0.96 – 2.68	1.53	0.91 – 2.56

FG : Fasting glucose

HR : Hazard ratio

CI : Confidence interval

a : per 1,000 person-years of follow-up

b : Adjusted for age and sex

c : Adjusted for age, sex, body mass index, systolic blood pressure, HDL cholesterol, LDL cholesterol, triglycerides, hypertension and hyperlipidemia status, cigarette smoking and alcohol intake categories.

**Table 3. Risk of Cerebral Infarction and Fasting Insulin Level**

	FI, mU/L	Subjects	Cases	Crude Incidence Rates <sup>a</sup>	Model 1 <sup>b</sup>		Model 2 <sup>c</sup>	
					HR	95% CI	HR	95% CI
Tertile 1	< 3.2	866	37	3.89	1.82	1.03 – 3.21	1.96	1.09 – 3.53
Tertile 2	3.2 – 5.3	847	18	1.91	1.00	Reference	1.00	Reference
Tertile 3	5.4 ≤	895	32	3.23	2.10	1.17 – 3.76	1.96	1.09 – 3.53

FI : Fasting insulin

HR : Hazard ratio

CI : Confidence interval

a : per 1,000 person-years of follow-up

b : Adjusted for age and sex

c : Adjusted for age, sex, body mass index, systolic blood pressure, HDL cholesterol, LDL cholesterol, triglycerides, hypertension and hyperlipidemia status, cigarette smoking and alcohol intake categories.

**Table 4. Crude Incidence Rates of Cerebral Infarction in the 9 groups**

Fasting Glucose, mg/dL	Fasting Insulin, mU/L		
	T1 (< 3.2)	T2 (3.2 – 5.3)	T3 (5.4 ≤)
T 1 (< 88)	Group 1	Group 2	Group 3
Subjects	325	271	199
Cases	16	3	4
Crude incidence rate <sup>a</sup>	4.42	0.99	1.77
T 2 (88 – 95)	Group 4	Group 5	Group 6
Subjects	308	288	290
Cases	9	4	10
Crude incidence rate <sup>a</sup>	2.66	1.25	3.10
T 3 (96 ≤)	Group 7	Group 8	Group 9
Subjects	233	288	406
Cases	12	11	18
Crude incidence rate <sup>a</sup>	4.81	3.45	4.07

T : tertile.

a : per 1,000 person-years of follow-up

in T3. In these analyses, HRs in T1 and T3 were higher than T2, but were not significant.

### FI and Risk of Cerebral Infarction

Table 3 shows crude incidence rates and HRs for cerebral infarction by tertiles of FI. Crude incidence rates of FI tertiles 1-3 were 3.89, 1.91 and 3.23 per 1,000 person-years. The tertile with the lowest risk of cerebral infarction was T2. Therefore, we defined T2 as the reference category.

In an age and sex-adjusted analysis (model 1), HRs were

1.82 (95% CI, 1.03 – 3.21) in T1 and 2.10 (95% CI, 1.17 – 3.76) in T3, using T2 as the reference. In multivariate-adjusted analysis (model 2), HRs for cerebral infarction were 1.96 (95% CI, 1.09 – 3.53) in T1 and 1.96 (95% CI, 1.09 – 3.53) in T3. In these analyses, HRs in T1 and T3 were significantly higher than T2.

### Risk of Cerebral Infarction in the 9 groups

Table 4 shows crude incidence rates in the 9 groups defined by tertiles of FG and FI. The crude incidence rates

of the 9 groups were 4.42 (G1), 0.99 (G2), 1.77 (G3), 2.66 (G4), 1.25 (G5), 3.10 (G6), 4.81 (G7), 3.45 (G8) and 4.07 (G9) per 1,000 person-years. The group with the lowest risk of cerebral infarction was G2. Therefore, we defined G2 as the reference group.

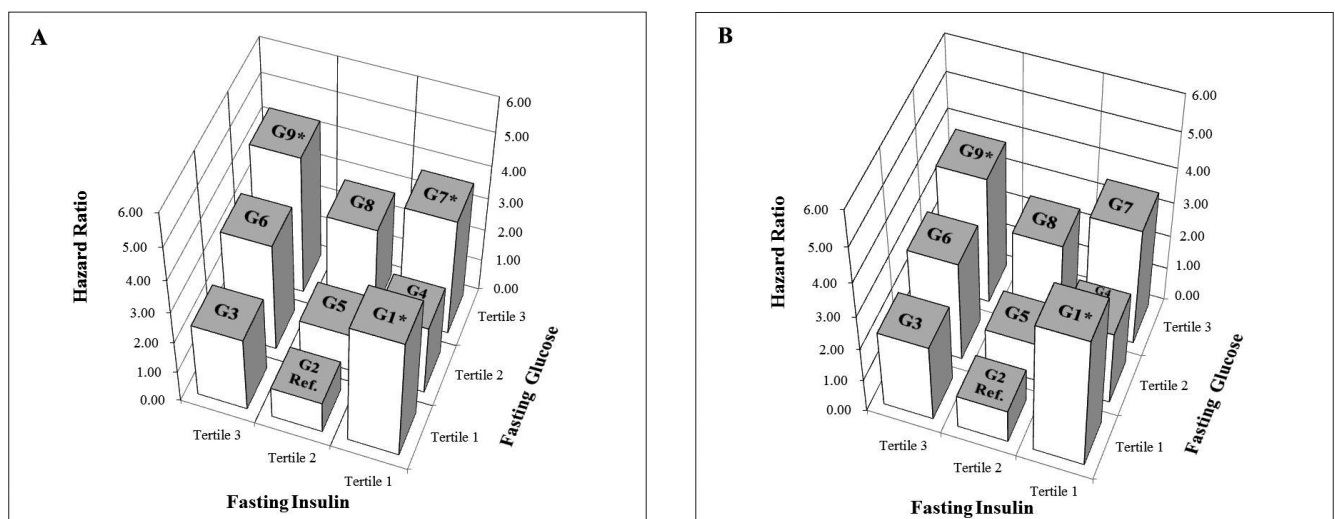
Figure 1 shows HRs of cerebral infarction in the 9 groups. In age and sex-adjusted analysis (Figure 1A), HRs of cerebral infarction were 3.78 (95% CI, 1.10 – 12.98) in G1, 2.36 (95% CI, 0.53 – 10.57) in G3, 2.19 (95% CI, 0.59 – 8.09) in G4, 1.21 (95% CI, 0.27 – 5.40) in G5, 3.41 (95% CI, 0.94 – 12.42) in G6, 3.66 (95% CI, 1.03 – 12.99) in G7, 2.73 (95% CI, 0.76 – 9.78) in G8 and 4.32 (95% CI, 1.27 – 14.71) in G9, respectively. In this analysis, HRs in G1, G7 and G9 were significantly higher than the G2 reference group. In multivariate-adjusted analysis (Figure 1B), HRs of cerebral infarction were 3.93 (95% CI, 1.13 – 13.72) in G1, 2.30 (95% CI, 0.51 – 10.34) in G3, 2.19 (95% CI, 0.58 – 8.19) in G4, 1.18 (95% CI, 0.26 – 5.31) in G5, 2.96 (95% CI, 0.81 – 10.88) in G6, 3.48 (95% CI, 0.97 – 12.53) in G7, 2.39 (95% CI, 0.66 – 8.62) in G8 and 3.73 (95% CI, 1.09 – 12.84) in G9, respectively. In this analysis, HRs in G1 and G9 were significantly higher than the G2 reference group.

In T2 and T3 of FI, risk of cerebral infarction increased according to FG level. In T1 of FI, a U-shaped relationship was seen between FG and risk of cerebral infarction. On the other hand, a U-shaped relationship was seen between FI and risk of cerebral infarction in each tertile of FG. G1, with the lowest FI level and lowest FG level, was an independent risk for cerebral infarction.

## Discussion

The present prospective study showed that the relation between FI level and risk of cerebral infarction was U-shaped and this relation was seen in each tertile of FG in a Japanese general population. This association was not substantially altered by adjustment for established cardiovascular risk factors like BMI, SBP, HDL cholesterol, LDL cholesterol, TG, hypertension medication, hyperlipidemia, cigarette smoking and alcohol intake habits. To the best of our knowledge, this is the first report that assessed the risk of cerebral infarction in 9 groups defined by tertile of FG and FI.

The relation between FI and stroke was examined in some previous studies. Folsom and colleagues, in the ARIC Study, reported there was positive association between a high FI level and the risk of stroke after adjustment for other cardiovascular risk factors<sup>9</sup>. Nakamura and colleagues reported that a positive relationship was shown between risk of stroke and FI in a prospective cohort study of middle-aged non-diabetic Japanese men<sup>6</sup>. One nested case control study, conducted in a nondiabetic population in northern Sweden, reported that a high FI level was positively and significantly associated with stroke<sup>13</sup>. Our results are consistent with the findings of these previous studies. An important finding of our study was that the group with lowest FI level in the lowest FG level was at risk of cerebral infarction, but there are no reports investigating the association between a low FI level and cerebral infarction, to our knowledge. The association of a low FI level with cerebral infarction has some indirect support from previously reported results. Wannamethee and colleagues<sup>14</sup>, in the British Regional



**Figure 1.**

A : Hazard ratios (HRs) of cerebral infarction in the 9 groups after adjustment for age and sex, using group 2 (G2) as the reference.

B : HRs of cerebral infarction in 9 groups after adjustment age, sex, body mass index, systolic blood pressure, HDL cholesterol, LDL cholesterol, triglycerides, hypertension and hyperlipidemia status, cigarette smoking and alcohol intake categories, using G2 as the reference. \* $p < 0.05$ . G indicates group. Ref. indicates reference.



Heart Study, reported that risk of stroke increased in the lowest nonfasting insulin quintile. In the Bruneck Study, it was reported that not only high FI levels, but also low FI levels were positively associated with risk of carotid atherosclerosis and coronary heart disease after adjustment for cardiovascular risk factors<sup>15, 16</sup>. In this study, the authors suggested a hypothesis that hypoinsulinemia leads to insufficient insulinization, despite the expected higher insulin sensitivity. Subsequently, hypoinsulinemia affects the function of specific cell types involved in the atherogenetic process and increases the risk of atherosclerosis. Other previous studies reported that atherosclerosis was associated with cerebral infarction<sup>17-19</sup>. Therefore, we suggest that a low FI level is associated with cerebral infarction. We reported that the relationship between IR measured by the HOMA-IR and cerebral infarction was not dose-dependent in a Japanese general population, which is the same population as in the present study<sup>8</sup>. We speculate that finding was associated with the U-shaped relationship between cerebral infarction and FI, which is an element of HOMA-IR, in each tertile of FG.

The present study has some limitations. Although the study subjects were selected from a population-based health check-up system, they were not selected at random and they lived in only 3 districts. Thus, the data may not be generalizable to other urban populations. In addition, single point data collection may have affected the results. We defined the group based on a single measurement of the FI and FG. It is possible that subjects with abnormal glucose tolerance are in the T1 and T2 of the FG, in which FG is normal. The present study has some strong points. First, it was a longitudinal population-based study. Second, the subjects were followed for more than 10 years and the follow-up rate was quite high. Third, diagnosis of stroke was made by an independent committee using accepted diagnostic criteria. Fourth, the blood samples were analyzed at a single laboratory using the same method of measurement, so we believe that the reliability of the data is high.

In conclusion, we showed that the association between FI and risk of cerebral infarction was U-shaped and this association was seen in each FG level in a Japanese general population. In addition, the group with the lowest FI level in the lowest FG level was at risk of cerebral infarction. However, it remains uncertain whether this association can be shown in other general populations. Future studies are needed to confirm the relation between FI level, FG level and risk of cerebral infarction events in other general populations and in other races.

#### Declaration of Conflicting Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication

of this article.

#### Acknowledgments

This study was supported by Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and by grants from the Foundation for the Development of the Community, Tochigi, Japan.

#### References

1. Moller DE, Flier JS. Insulin resistance—mechanisms, syndromes, and implications. *N Engl J Med* 1991 ; 325 : 938-948.
2. Kernan WN, Inzucchi SE, Viscoli CM, et al. Insulin resistance and risk for stroke. *Neurology* 2002 ; 59 : 809-815.
3. Bravata DM, Wells CK, Kernan WN, et al. Association between impaired insulin sensitivity and stroke. *Neuroepidemiology* 2005 ; 25 : 69-74.
4. Park HY, Kyeong H, Park DS, et al. Correlation between insulin resistance and intracranial atherosclerosis in patients with ischemic stroke without diabetes. *J Stroke Cerebrovasc Dis* 2008 ; 17 : 401-405.
5. Rundek T, Gardener H, Xu Q, et al. Insulin resistance and risk of ischemic stroke among nondiabetic individuals from the northern Manhattan study. *Arch Neurol* 2010 ; 67 : 1195-1200.
6. Nakamura K, Sakurai M, Miura K, et al. Homeostasis model assessment of insulin resistance and the risk of cardiovascular events in middle-aged non-diabetic Japanese men. *Diabetologia* 2010 ; 53 : 1894-1902.
7. Shinozaki K, Naritomi H, Shimizu T, et al. Role of insulin resistance associated with compensatory hyperinsulinemia in ischemic stroke. *Stroke* 1996 ; 27 : 37-43.
8. Kaneda Y, Ishikawa S, Sadakane A, et al. Insulin Resistance and Risk of Cerebral Infarction in a Japanese General Population : The Jichi Medical School Cohort Study. *Asia Pac J Public Health* 2013.
9. Folsom AR, Rasmussen ML, Chambless LE, et al. Prospective associations of fasting insulin, body fat distribution, and diabetes with risk of ischemic stroke. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Diabetes Care* 1999 ; 22 : 1077-1083.
10. Lakka HM, Lakka TA, Tuomilehto J, et al. Hyperinsulinemia and the risk of cardiovascular death and acute coronary and cerebrovascular events in men : the Kuopio Ischaemic Heart Disease Risk Factor Study. *Arch Intern Med* 2000 ; 160 : 1160-1168.
11. Ishikawa S, Gotoh T, Nago N, et al. The Jichi Medical School (JMS) Cohort Study : design, baseline data and standardized mortality ratios. *J Epidemiol* 2002 ; 12 : 408-417.

12. Ishikawa S, Kayaba K, Gotoh T, et al. Metabolic syndrome and C-reactive protein in the general population : JMS Cohort Study. *Circ J* 2007 ; 71 : 26-31.
13. Lindahl B, Dinesen B, Eliasson M, et al. High proinsulin levels precede first-ever stroke in a nondiabetic population. *Stroke* 2000 ; 31 : 2936-2941.
14. Wannamethee SG, Perry IJ, Shaper AG. Nonfasting serum glucose and insulin concentrations and the risk of stroke. *Stroke* 1999 ; 30 : 1780-1786.
15. Bonora E, Willeit J, Kiechl S, et al. Relationship between insulin and carotid atherosclerosis in the general population. The Bruneck Study. *Stroke* 1997 ; 28 : 1147-1152.
16. Bonora E, Willeit J, Kiechl S, et al. U-shaped and J-shaped relationships between serum insulin and coronary heart disease in the general population. The Bruneck Study. *Diabetes Care* 1998 ; 21 : 221-230.
17. Cohen A, Tzourio C, Bertrand B, et al. Aortic plaque morphology and vascular events : a follow-up study in patients with ischemic stroke. FAPS Investigators. French Study of Aortic Plaques in Stroke. *Circulation* 1997 ; 96 : 3838-3841.
18. Hollander M, Bots ML, Del Sol AI, et al. Carotid plaques increase the risk of stroke and subtypes of cerebral infarction in asymptomatic elderly : the Rotterdam study. *Circulation* 2002 ; 105 : 2872-2877.
19. Hollander M, Hak AE, Koudstaal PJ, et al. Comparison between measures of atherosclerosis and risk of stroke : the Rotterdam Study. *Stroke* 2003 ; 34 : 2367-2372.

# 空腹時インスリン濃度と空腹時血糖による脳梗塞発症のリスク評価：JMS コホート研究より

兼田 裕司<sup>1</sup>, 石川 鎮清<sup>2</sup>, 後藤 忠雄<sup>3</sup>, 萱場 一則<sup>4</sup>, 安田 是和<sup>1</sup>, 梶井 英治<sup>2</sup>

<sup>1</sup>自治医科大学 消化器・一般外科, 〒320-0498 栃木県下野市薬師寺3311-1

<sup>2</sup>自治医科大学 地域医療学教室

<sup>3</sup>国民健康保険和良診療所

<sup>4</sup>埼玉県立大学 健康開発学科

## 要 約

JMSコホート研究のデータを用いて、空腹時インスリン濃度（FI）、空腹時血糖（FG）と脳梗塞発症との関係について検討した。JMSコホート研究参加者の中で、FI、FGを測定しており、脳卒中、心筋梗塞の既往があるもの、糖尿病治療中のものを除外した2608例を対象とした。FI、FGをそれぞれ3分位に分け、FIが第1分位（T1）、FGがT1の群をGroup 1（G1）、FIがT2、FGがT1の群をG2、FIがT3、FGがT1の群をG3、FIがT1、FGがT2の群をG4、FIがT2、FGがT2の群をG5、FIがT3、FGがT2の群をG6、FIがT1、FGがT3の群をG7、FIがT2、FGがT3の群をG8、FIがT3、FGがT3の群をG9とした。統計学的手法としてCoxの比例ハザードモデルを用いた。G2を基準として脳梗塞発症のハザード比、95%信頼区間を計算したところ、G1、G3、G4、G5、G6、G7、G8、G9はそれぞれ3.93（1.13–13.72）、2.30（0.51–10.34）、2.19（0.58–8.19）、1.18（0.26–5.31）、2.96（0.81–10.88）、3.48（0.97–12.53）、2.39（0.66–8.62）、3.73（1.09–12.84）であった。脳梗塞発症とFIとの関係はFGの各レベルでU字型となっていた。

（キーワード：脳梗塞、空腹時インスリン濃度、空腹時血糖、コホート研究）