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ORIGINAL ARTICLES

Fasting insulin and risk of cerebral infarction in a Japanese general population: The Jichi Medical School Cohort Study

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Abstract

Objective: We investigated the relation between fasting insulin (FI) and risk of cerebral infarction in a Japanese general population. *Methods:* The subjects were 2,610 men and women without past history of stroke or myocardial infarction and under treatment for diabetes, examined between 1992 and 1995 as part of the Jichi Medical School Cohort Study. The FI level was measured once at the baseline. Subjects were divided into quintiles by FI levels, and Cox's proportional hazard model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for cerebral infarction. *Results:* During an average of 11.1 years of follow-up, 87 participants developed cerebral infarction. Crude incidence rates of FI quintiles 1-5 were 4.69, 2.35, 1.85, 2.77 and 3.30 per 1,000 person-years, respectively. The multivariate-adjusted HRs for cerebral infarction were 2.33 (95% CI, 1.10 – 4.96) in quintile 1 (Q1), 1.25 (95% CI, 0.55 – 2.84) in Q2, 1.68 (95% CI, 0.76 – 3.70) in Q4 and 2.06 (95% CI, 0.94 – 4.47) in Q5, using Q3 as the reference.
Conclusions: The lowest FI level was associated with increased risk of cerebral infarction and the association between FI and risk of cerebral infarction appeared to be a U-shaped relationship.

INTRODUCTION

Insulin resistance is defined as a state of subnormal biologic response to a given concentration of insulin, and it is well established that insulin resistance is independently associated with risk of stroke.[1-6] To assess insulin resistance, several indices have been used, such as the homeostasis model assessment[1,3-5], but it is rare to use fasting insulin (FI) solely. The relation between FI and stroke was investigated in several prospective studies, but this relation is controversial.[3,7,8] In addition, little is known about the relationship between FI and the risk of cerebral infarction in a Japanese general population.[3] The purpose of this study was to examine the relationship between insulin resistance measured by FI and cerebral infarction in a Japanese general population in a prospective study.

METHODS

Subjects

The Jichi Medical School (JMS) Cohort Study is a prospective study that began in 1992 with the aim of investigating risk for cardiovascular disease in a Japanese population. Details of the JMS Cohort Study design and some descriptive data have been published previously.[9,10] 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

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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%.

FI level was measured once at the baseline in three communities (Wara, Takasu and Sakuma) as an optional examination that included 3,100 subjects (1,338 men and 1,762 women).

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 blood samples could not be obtained (n = 26), who did not respond to questions about past history of stroke, myocardial infarction, diabetes mellitus, alcohol consumption or smoking habit (n = 251), and whose data about physical findings were incomplete (n = 101). Finally, 2,610 subjects (1,097 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 a seated subject who had rested in the sitting position for five minutes before the measurement. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Triglycerides (TG) were measured by an enzymatic method (Wako, Osaka, Japan; interassay coefficient of variation (CV): 1.7%). HDL cholesterol was measured using the phosphotungstate precipitation method (Wako, Osaka, Japan; interassay CV: 1.9%). Fasting glucose (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.

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 them in the present study by means of a health examination program in each community. If they had a history of such disease, 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 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, composed of 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 ± standard deviation (SD), except for TG and FG. The distributions of TG and FG 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.

Smoking status and drinking status were compared using the chi-square test. Multiple group comparisons were evaluated by the Kruskal-Wallis test. To investigate the risk of cerebral infarction associated with the FI, we divided the participants into five equal groups according to the quintiles of FI levels. Cutoffs of quartiles for the FI were 2.5, 3.7, 4.9 and 7.1. Crude incidence rates of cerebral infarction were calculated per 1,000 person-years. We used a Cox's proportional hazard model to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for cerebral infarction with FI quintiles. HRs and 95% CIs were first calculated after adjustment for age and then for age, SBP, smoking status, drinking status, HDL cholesterol, and BMI. The quintile 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 PASW Statistics 18 (SPSS Inc, Japan).

RESULTS

During a mean follow-up of 11.1 years (Men, 10.9 years; Women, 11.2 years), 87 of 2,610 participants developed cerebral infarction (men, 46 cases; women, 41 cases).

Baseline characteristics

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

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Table 2 shows crude incidence rates and HRs for cerebral infarction by quintiles of FI. Crude incidence rates of FI quintiles 1-5 were 4.69, 2.35, 1.85, 2.77 and 3.30 per 1,000 person-years. The quintile with the lowest risk of cerebral infarction was Q3. Therefore, we defined Q3 as the reference category.

In age and sex-adjusted analysis (model 1), HRs for cerebral infarction were 2.11 (95% CI, 1.02 – 4.37) in Q1, 1.23 (95% CI, 0.54 – 2.77) in Q2, 1.70 (95% CI, 0.77 – 3.75) in Q4 and 2.29 (95% CI, 1.06 – 4.95) in Q5, using Q3 as the reference. In this analysis, HR in Q1 and Q5 were significantly higher than Q3. In multivariate-adjusted analysis (model 2), HRs for cerebral infarction were 2.33 (95% CI, 1.10 – 4.96) in Q1, 1.25 (95% CI, 0.55 – 2.84) in Q2, 1.68 (95% CI, 0.76 – 3.70) in Q4 and 2.06 (95% CI, 0.94 – 4.47) in Q5. In this analysis, HR in Q1 was significantly higher than Q3, and HR in Q5 was higher than Q3, but not significantly. A U-shaped relationship was seen between FI and risk of cerebral infarction and this relationship did not change after adjustment for several cardiovascular risk factors.

We performed the same analyses in other stroke subtypes (intracerebral hemorrhage, subarachnoid hemorrhage), but there were no significant differences between the quintiles in terms of FI (data not shown).

DISCUSSION

The present prospective study found a positive relationship between the lowest quintile of FI and the risk of cerebral infarction, while a U-shaped relation was seen between FI and the risk of cerebral infarction in a Japanese general population. This association was not substantially altered by adjustment for established cardiovascular risk factors like BMI, SBP, HDL cholesterol, cigarette smoking and alcohol intake habits.

The relation between FI and stroke was examined in some previous studies. Folsom *et al.*[7], in the ARIC Study, reported there was positive association between high FI levels and the risk of stroke after adjustment for other cardiovascular risk factors. Nakamura *et al.*[3] 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. One nested case control study conducted in a nondiabetic population in northern Sweden reported that a high FI level was significantly positively associated with stroke.[11] Our results are consistent with the findings of these previous studies, although there was no statistically significant relation between the highest quintile of FI and risk of cerebral infarction after adjustment for other cardiovascular risk factors. An important finding of our study was that the lowest FI level increased the risk of cerebral infarction, but we found no reports investigating directly the association between a low FI level and cerebral infarction. The association of a low FI level with cerebral infarction has some indirect support from previously reported results. Wannamethee *et al.*[12], in the British Regional 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

Table 1: Baseline characteristics of the study population

		Fasting insulin, mU/L					
	Total	**Q 1 (< 2.5)**	**Q 2 (2.5 – 3.6)**	**Q 3 (3.7 – 4.8)**	**Q 4 (4.9 – 7.0)**	**Q 5 (7.1 ≤)**	**P value**
Subjects	**2610**	**552**	**536**	**484**	**520**	**518**	
Age, years	57.3 ± 11.9	59.0 ± 11.6	58.4 ± 11.0	56.7 ± 12.6	56.4 ± 12.0	55.7 ± 11.8	< 0.001
sex, men/women	1097/1513	345/207	221/315	182/302	177/343	172/346	< 0.001
Current smoking, %	22.5	36.6	20.5	19.0	19.4	16.0	< 0.001
Current alcohol drinking, %	49.9	61.1	49.6	48.3	46.2	43.6	< 0.001
Body mass index, kg/m2	22.8 ± 3.0	21.0 ± 2.4	22.1 ± 2.5	22.8 ± 2.5	23.6 ± 2.9	24.5 ± 3.3	< 0.001
Systolic blood pressure, mm Hg	130.2 ± 22.0	124.9 ± 21.8	128.9 ± 21.9	130.5 ± 21.8	132.4 ± 21.1	134.6 ± 22.2	< 0.001
Diastolic blood pressure, mm Hg	77.3 ± 12.7	74.2 ± 11.9	76.7 ± 12.7	77.4 ± 12.9	78.2 ± 12.2	80.1 ± 13.0	< 0.001
HDL cholesterol, mg/dL	49.8 ± 12.6	54.5 ± 13.7	50.6 ± 12.0	49.6 ± 12.3	48.5 ± 11.8	45.3 ± 11.3	< 0.001
Triglycerides, mg/dL	89 (66 – 123)	75 (59 – 102)	84 (62– 115)	86 (65 – 120)	94 (70 – 132)	108 (82 – 147)	< 0.001
Fasting glucose, mg/dL	92 (86 – 99)	89 (84 – 95)	91 (86 – 97)	91 (86 – 99)	93 (87 – 99)	95 (89 – 104)	< 0.001

Values represent mean ± SD or percent except for triglycerides and fasting glucose, for which median and interquartile range are shown.
Q: quintile.

Table 2: Risk of cerebral infarction and fasting insulin level

		Fasting insulin, mU/L				
	Total	**Q 1 (< 2.5)**	**Q 2 (2.5 – 3.6)**	**Q 3 (3.7 – 4.8)**	**Q 4 (4.9 – 7.0)**	**Q 5 (7.1 ≤)**
Subjects	**2610**	**552**	**536**	**484**	**520**	**518**
Number of events	87	28	14	10	16	19
Crude incidence rate[a]	3.02	4.69	2.35	1.85	2.77	3.30
HR (95% CI) in model 1[b]		2.11 (1.02 – 4.37)	1.23 (0.54 – 2.77)	1.00 (Reference)	1.70 (0.77 – 3.75)	2.29 (1.06 – 4.95)
HR (95% CI) in model 2[c]		2.33 (1.10 – 4.96)	1.25 (0.55 – 2.84)	1.00 (Reference)	1.68 (0.76 – 3.70)	2.06 (0.94 – 4.47)

Q: quintile.
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, serum HDL cholesterol, cigarette smoking and alcohol intake category.

low FI levels were positively associated with risk of carotid atherosclerosis and coronary heart disease after adjustment for cardiovascular risk factors.[13,14] In this study, the authors suggested a hypothesis that hypoinsulinemia leads to insufficient insulinization, despite the expected higher insulin sensitivity.

The association of a high FI level with cerebral infarction is suggested by a lot of evidence from previously reported results. In a nested case control study, FI in patients with intracranial or extracranial atherosclerosis was significantly higher than FI in patients without atherosclerosis.[4] In a cross-sectional study, a positive correlation was seen between FI and carotid intimal-medial wall thickness.[15] In a basic study, there was a positive relation between long-term insulin injection and thickness of the aorta intima in rats.[16] Two cohort studies reported that carotid atherosclerosis was associated with the risk of cerebral infarction.[17,18] Therefore, we assume that high insulin levels cause carotid atherosclerosis and contribute to the development of cerebral infarction.

Previous studies reported that FI correlated positively with fibrinogen[19,20] and plasminogen activator inhibitor type 1 (PAI-1) activity.[19,21,22] Other previous studies reported that elevated fibrinogen levels[23,24] and PAI-1 activity levels[25,26] were associated with cerebral infarction. Therefore, we assume high FI levels induce high fibrinogen levels and PAI-1 activity levels and lead to the development of cerebral infarction. On the other hand, it is unknown why a low FI level is associated with cerebral infarction.

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. There are some strong points in the present study. 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 measurement method, so we believe that the reliability of the data is high.

In conclusion, we showed that a low FI level is associated with increased risk of cerebral infarction and that the association between FI and risk of cerebral infarction appears to be U-shaped in a Japanese general population. However, it remains uncertain whether a low FI level is an independent risk of cerebral infarction in other general populations. Future studies are needed to confirm the relation between a low FI level and cerebral infarction events in other general populations.

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DISCLOSURE

Conflict of interest: None

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