Prevalence of Abnormal Glucose Metabolism and Insulin Resistance Among Subtypes of Ischemic Stroke in Japanese Patients

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Background and Purpose—The purpose was to assess the prevalence of disorders of glucose metabolism and insulin resistance in Japanese ischemic stroke patients with no history of diabetes by performing 75-gram oral glucose tolerance test (OGTT).

Methods—We recruited 427 ischemic stroke patients (atherothrombotic infarction, n=220; lacunar infarction, n=125; cardioembolic infarction, n=82). OGTT was used to evaluate disorders of glucose metabolism in stroke patients without previously known diabetes (n=113). We investigated the relationships among the prevalence of abnormal glucose metabolism, ischemic stroke subtypes, and the prevalence of insulin resistance using homeostasis model assessment for insulin resistance and immunoreactive insulin at 120 minutes after glucose loading (IRI$_{120}$).

Results—OGTT identified the presence of disorders of glucose metabolism in 62.8% of ischemic stroke patients without previously known diabetes, including diabetes (24.8%) and impaired glucose tolerance (lone impaired glucose tolerance and impaired fasting glucose plus impaired glucose tolerance, 34.5%). The prevalence of newly diagnosed diabetes and impaired glucose tolerance was the highest in the atherothrombotic infarction group (68.9%). The highest values of homeostasis model assessment for insulin resistance and immunoreactive insulin at 120 minutes after glucose loading were found in atherothrombotic infarction patients with abnormal glucose tolerance.

Conclusions—In this study, a significantly large percentage of Japanese patients with ischemic stroke and no history of diabetes were found to have disorders of glucose metabolism by OGTT. Impaired glucose tolerance and insulin resistance could play an important pathogenic role in the development of atherothrombotic infarction. (Stroke. 2009;40:1289-1295.)

Key Words: atherothrombotic infarction ■ diabetes mellitus ■ impaired glucose tolerance ■ insulin resistance ■ ischemic stroke

Stroke is the major cause of mortality and the third leading cause of death in Japan. Cerebral hemorrhage was the most common type of stroke in Japan in the 1960s. However, the incidence of ischemic stroke (cerebral infarction) has been increasing in recent years among the stroke subtypes. Currently, it is the most common type of stroke in Japan. Although risk factors are different among the subtypes of cerebral infarction (atherothrombotic infarction, lacunar infarction, and cardioembolic infarction), it is well known that diabetes mellitus is a major independent risk factor for stroke, in addition to hypertension and dyslipidemia. In Japan, the recent estimate of patients afflicted with diabetes is >7 million, and the number increases to 20 million when subjects with impaired glucose tolerance (IGT) are included.

IGT is regarded as the preliminary stage before the onset of diabetes and is characterized by impaired insulin secretion or insulin sensitivity. More importantly, subjects with IGT are at risk for cardiovascular disease. Asian populations including Japanese tend to have weaker efficiency of insulin secretion than other races. Even if the insulin resistance is not worse than that in whites, it is easy for Asians to have glucose intolerance. The 75-gram oral glucose tolerance test (OGTT) measures immunoreactive insulin (IRI) and is useful for evaluating abnormal glucose metabolism (AGM) and insulin resistance. A Japanese population study found a high prevalence of AGM in OGTT in patients with acute coronary syndrome with previously undiagnosed diabetes. In Japan, the prevalence of diabetes in stroke patients is <40%. From the point of view of indirect prevention of stroke, it is important to evaluate the exact prevalence of AGM in patients with ischemic stroke using OGTT. Previous studies demonstrated high prevalences of AGM including IGT in...
European, American, and Chinese stroke patients based on the results of OGTT.9–12 However, to our knowledge, there is no report that assessed the prevalence of newly diagnosed AGM in ischemic stroke Japanese patients with previously undiagnosed diabetes. In addition, there are no data on the prevalence of diabetes and IGT in patients with ischemic stroke.

The purpose of this retrospective study was to assess the prevalence of OGTT-based AGM in Japanese patients with ischemic stroke with undiagnosed diabetes. The study was also designed to define the relationship between insulin resistance and ischemic stroke by using homeostasis model assessment for insulin resistance (HOMA-IR) and IRI level at 120 minutes after glucose loading (IRI120) as indexes of insulin resistance.

Materials and Methods

Subjects
The study encompassed 427 Japanese patients with ischemic stroke who were admitted to Juntendo University Hospital or Juntendo University Shizuoka Hospital between April 2005 and October 2006. Brain CT or brain MRI and electrocardiography were performed in all patients. Based on the Classification of Cerebrovascular Disease III by the committee of the National Institute of Neurological Disorders and Stroke, as well as the diagnostic criteria of the Trial of Org 10172 in Acute Stroke Treatment study13 for cerebral infarction subtypes, ischemic stroke was divided into 3 clinical subtypes: (1) atherothrombotic infarction (ATI); (2) lacunar infarction (LI); and (3) cardioembolic infarction (CE). Patients with other stroke subtypes were excluded, including patients with transient ischemic attack, cerebral hemorrhage, dissection, and vasculitis/collagen disease.

Blood samples for the diagnosis of diabetes were taken after determination of the clinical subtype of stroke, and the mean interval between the onset of stroke and diagnosis of diabetes was 14.3 ± 1.8 days. Informed consent was obtained from all subjects after they received a full explanation of the study. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or antihypertensive treatment. Dyslipidemia was defined as LDL cholesterol ≥ 140 mg/dL or triglycerides ≥ 150 mg/dL or use of lipid-lowering medication. The Ethics Committee of Juntendo University approved this study.

OGTT
A standard OGTT with 75 grams of glucose was performed at least 2 weeks after admission to minimize any possible confounding effects of acute stroke on blood glucose. Blood samples to determine plasma glucose and insulin concentrations were taken at 0, 30, 60, 90, and 120 minutes after the glucose load. Interpretation of the OGTT results was based on the World Health Organization definition,14 also using the concept of impaired fasting glucose included in the American Diabetes Association criteria.15 In brief, patients were classified as diabetics when fasting plasma glucose (FPG) was ≥ 126 mg/dL, or HbA1c ≥ 6.5%, or history of using insulin or oral hypoglycemic agents, or when plasma glucose at 2-hour OGTT was ≥ 200 mg/dL. IGT was defined as FPG level of 110 to 125 mg/dL and 2-hour OGTT plasma glucose level of 140 to 199 mg/dL. Subjects with IGT were further subclassified into those with normal FPG level (designated as lone IGT) and those with FPG level of 110 to 125 mg/dL (designated as impaired fasting glucose plus IGT). Thus, patients with impaired fasting glucose had FPG level of 110 to 125 mg/dL and 2-hour OGTT plasma glucose level of < 140 mg/dL. Patients with normal glucose tolerance (NGT) had FPG level of < 110 mg/dL (designated as lone IGT) and those with FPG level of 110 to 125 mg/dL (designated as impaired fasting glucose plus IGT). Then, patients with impaired fasting glucose had FPG level of 110 to 125 mg/dL and 2-hour OGTT plasma glucose level of < 140 mg/dL.

The HOMA-IR, an indirect index of insulin resistance, was calculated as fasting plasma insulin (µU/mL)/fasting plasma glucose (mg/dL)/405. HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were measured on the first morning after admission.

Statistical Analyses
All values presented in this study are expressed as mean ± SD. Differences in mean values of groups were tested for significance by 1-way ANOVA followed by posthoc Fisher protected least significant difference test. Differences in proportions were tested by χ² test. Data were analyzed using StatView version 5.0 software package (Abacus Concept, Inc). P < 0.05 denoted the presence of statistically significant difference.

Figure 1. A, Flow chart graph describing enrollment of patients with ischemic stroke in the present study and those who underwent OGTT. B, Numbers of patients with disorders of glucose metabolism according to the values of FPG and plasma glucose concentrations at 2 hours after OGTT. IFG indicates impaired fasting glucose.
Results

Prevalence of AGM

We studied 427 ischemic stroke patients with a mean age of 71.1±11.5 years. Hypertension, diabetes, dyslipidemia, and current smoking were observed in 71.4%, 36.3%, 43.3%, and 23.2% of the patients, respectively. The mean HbA1c level at admission was 6.01±1.52%. Among these patients, 155 patients with a previous diagnosis of type 2 diabetes (FPG ≥126 mg/dL or HbA1c ≥6.5%) were not subjected to OGTT. Functional recovery was evaluated in all patients by the modified Rankin Scale, and swallowing function was tested in patients with dysphasia by swallowing test. Patients with a modified Rankin Scale ≥3 or impaired swallowing function were excluded from the study. Thus, among 272 patients without previously known diabetes, OGTT was performed in 113 (41.5%) patients (ATI, n=63; LI, n=38; CE, n=12; Figure 1A). These subjects had a normal HbA1c level (Table 1).

Analysis of ischemic stroke patients who underwent OGTT (n=113) showed 96 (85%) patients had normal FPG (<110 mg/dL), but among them 38 (39.6%) patients had IGT and 16 (16.7%) patients had diabetes, based on 75-gram OGTT (Figure 1B). Furthermore, 71 (62.8%) patients had AGM (FPG ≥110 mg/dL and 2-hour OGTT plasma glucose of ≥140 mg/dL; Figure 1B), including 39 patients with IGT (34.5%) and 28 patients with diabetes (24.8%). Among the IGT subjects, 38 (97.4%) had normal FPG levels, with only 1 (2.6%) patient with impaired fasting glucose/IGT. Four patients had lone impaired fasting glucose pattern.

Clinical Characteristics of Patients With NGT, IGT, and Diabetes

Table 2 shows the clinical characteristics of the patients who underwent OGTT and were diagnosed with NGT, IGT, or diabetes. The LDL cholesterol, HDL cholesterol, and triglyceride levels were not different in the 3 groups. The proportion of patients with hypertension was higher in the IGT group (82.1%) than in the NGT and diabetes groups. However, systolic and diastolic blood pressure values were not significantly different in the 3 groups. The mean HbA1c was lowest in NGT subjects and highest in diabetes subjects (P<0.01).

Prevalence and Characteristics of AGM Among Ischemic Stroke Subtypes

Figure 2 shows the frequency of AGM in patients with each subtype of ischemic stroke. The prevalence of abnormal glucose tolerance (previously diagnosed diabetes, newly diagnosed diabetes, newly diagnosed IGT, and impaired FPG) was the highest in the ATI group (88.2%). Table 3 lists the clinical features of patients with ischemic stroke according to glucose tolerance and stroke subtype. Hypertension was more common in LI patients with AGM than in those with ATI and AGM or CE with AGM (P<0.05). The systolic and diastolic blood pressure values were not significantly different among the ischemic stroke subtypes. The mean HbA1c in ischemic stroke patients with AGM was the highest in the ATI group, followed by the LI and CE groups (ATI, 5.34±0.61%; LI, 5.29±0.49%; CE, 5.17±0.49; P<0.01; ATI vs CE). LDL cholesterol, HDL cholesterol, and triglyceride levels were not different among the 3 groups. All ischemic stroke patients received the best available treatment. Thus, all patients with ATI and LI were administered antiplatelet agents (eg, aspirin or cilostazol), and all patients with CE were administered...
anticoagulants (warfarin) (Table 3). The majority of patients with hypertension were administered antihypertensive medications (eg, angiotensin II type 1 receptor blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers), and most patients with dyslipidemia were also administered lipid-lowering agents (statins). There were no differences in each ischemic stroke subtype with AGM or with NGT.

**OGTT Patterns**

Figures 3A and 3B show the plasma glucose and insulin concentrations during OGTT according to stroke subtype. The plasma glucose levels were similar throughout the test period in ATI, LI, and CE subjects. However, insulin concentrations were lower in the CE subjects than other groups throughout the test period, except for the value at 90 minutes.

**Insulin Resistance Based on HOMA-IR and IRI_{120} After Glucose Loading**

Among the patients who underwent OGTT, the mean HOMA-IR was significantly higher in the diabetes subjects ($P<0.01$) than in NGT and IGT subjects (1.58±1.05; Table 2). The value of IRI$_{120}$ was significantly higher in diabetes subjects and IGT subjects (86.6±53.3) than in NGT subjects ($P<0.001$; Table 2). Further analysis showed that the mean HOMA-IR was significantly higher in the ATI group with AGM than in other stroke subtypes ($P<0.01$; Table 3). IRI$_{120}$ was also the highest in ATI with AGM (ATI, 84.7±55.9 μU/mL; LI, 75.7±41.9 μU/mL; CE, 66.6±32.8 μU/mL; Table 3).

**Discussion**

In the present study, we assessed the prevalence of disorders of glucose metabolism based on 75-gram OGTT in ischemic stroke patients without a previous diagnosis of diabetes. Our study demonstrated a high prevalence of AGM in Japanese patients with ischemic stroke, as was previously reported for patients with acute coronary syndrome in a Japanese popu-
A few published studies have used OGTT to test stroke patients who were not previously known to have diabetes, and a high prevalence of diabetes and IGT (including impaired fasting glucose and impaired fasting glucose plus IGT) was found.9–12 All of these studies have described the importance of performing OGTT to detect new cases of glucose intolerance among stroke patients without a previous diagnosis of diabetes. To our knowledge, our study is the first report that describes a high prevalence of disorders of glucose metabolism in Japanese patients with ischemic stroke.

The Hisayama study in Japan indicated that IGT, in addition to diabetes, is a risk factor for stroke.16 Our study showed a higher prevalence of IGT than diabetes, and that such prevalence was highest in patients with ATI among the subtypes of ischemic stroke. It is well known that IGT is a risk for subsequent development of diabetes and is the leading cause of cardiovascular disease.17 Moreover, previous studies demonstrated that IGT is associated with the increased carotid intima-media thickness, a representative clinical finding related to atherosclerosis.18–20 IGT may

### Table 3. Glucose Intolerance According to Subtype of Ischemic Stroke

<table>
<thead>
<tr>
<th></th>
<th>ATI (n=63)</th>
<th>LI (n=38)</th>
<th>CE (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AMG (n=44)</td>
<td>NGT (n=19)</td>
<td>AMG (n=21)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>69.1 ± 10.4</td>
<td>66.8 ± 13.1</td>
<td>69.6 ± 10.5</td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>32/12</td>
<td>14/5</td>
<td>12/9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33 (75.0%)</td>
<td>13 (68.4%)</td>
<td>20 (95.2%)§</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>26 (59.1%)</td>
<td>12 (63.2%)</td>
<td>12 (57.1%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>14 (31.8%)</td>
<td>9 (47.4%)</td>
<td>8 (38.1%)</td>
</tr>
<tr>
<td>Hypertension + dyslipidemia</td>
<td>19 (43.2%)</td>
<td>8 (42.1%)</td>
<td>11 (52.5%)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.34 ± 0.61*¶</td>
<td>5.06 ± 0.36</td>
<td>5.29 ± 0.49</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.01 ± 1.38*¶</td>
<td>1.29 ± 0.67</td>
<td>1.80 ± 1.10*§</td>
</tr>
<tr>
<td>IRI120, μU/mL</td>
<td>84.7 ± 55.9†</td>
<td>36.8 ± 24.5</td>
<td>75.7 ± 41.9†</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>141.5 ± 12.2</td>
<td>140.6 ± 13.0</td>
<td>140.0 ± 12.8</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>90.2 ± 7.7</td>
<td>89.8 ± 5.9</td>
<td>89.8 ± 6.5</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>48 ± 14</td>
<td>50 ± 12.2</td>
<td>52 ± 12</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>124 ± 38</td>
<td>131 ± 37.7</td>
<td>124 ± 20</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>122 ± 45.5</td>
<td>127 ± 78.7</td>
<td>137 ± 55.5</td>
</tr>
</tbody>
</table>

Data are mean ± SD or n (%).
*P < 0.05 vs NGT.
†P < 0.01 vs NGT.
‡P < 0.001 vs NGT.
§P < 0.05 vs CE.
||P < 0.01 vs CE.

The present study also demonstrated a higher prevalence of glucose abnormality in ATI patients with previously undiagnosed diabetes than in those with other types of ischemic stroke. A previous hospital-based study reported that the prevalence of diabetes was < 40% in stroke patients.8 Similar to that study, our results showed a prevalence of 36.3% based on laboratory data other than OGTT. However, our study revealed that the actual prevalence of AGM in ischemic stroke patients is much higher (60.0%) when assessed by OGTT.

Figure 3. Changes in (A) plasma glucose and (B) immunoreactive insulin concentrations during the 75-gram oral glucose load. Data are mean ± SD.
accelerate the atherosclerotic process of large cerebral arteries and carotid arteries, resulting in atherothrombotic infarction. In fact, our results indicated the highest prevalence of IGT in ATI patients. In our patients, IGT was diagnosed in 38% of ischemic stroke patients who underwent OGTT, and patients with ATI accounted for 61.5% of the IGT patients. These results also support the tight link between IGT and progression of atherosclerosis. Furthermore, Vermeer et al recently reported that IGT is an independent risk factor for future stroke in nondiabetic patients with transient ischemic attacks or minor ischemic stroke. Considered together, these studies and our results suggest that screening for AGM by OGTT is important for secondary prevention of stroke.

Previous studies showed that insulin resistance is associated with hyperinsulinemia in Japanese patients with atherothrombotic infarction. Although insulin resistance seems to be related to hypertension and dyslipidemia, our study indicated that age, systolic and diastolic blood pressure, and serum lipids were not different across the groups of various glucose levels. Matsumoto et al evaluated the correlation between insulin resistance and classic risk factors in type 2 diabetes patients with various subtypes of ischemic stroke by using the K index of the insulin tolerance test. In their results, hyperinsulinemia as a surrogate marker for insulin resistance was a risk factor for ATI. They suggested that insulin resistance predisposes patients with type 2 diabetes to ischemic stroke. In the present study, we evaluated insulin resistance by calculating HOMA-IR and IRI. Our results showed significantly higher IRI in ATI and LI patients with AGM compared with NGT patients, although this tendency could not be confirmed in patients with CE. Our data suggest that insulin resistance seems to be an important risk factor for thrombotic ischemic stroke.

Because the prevalence of IGT is high in ischemic stroke patients and insulin resistance is associated with atherothrombotic infarction, early intervention and treatment of insulin resistance seems to be important for the secondary prevention of stroke. Pioglitazone is a peroxisome proliferator-activated receptor- agonist and is used for insulin resistance. The PROactive study, a prospective, randomized, double-blind, placebo-controlled study in high-risk patients with type 2 diabetes and history of macrovascular disease, revealed that pioglitazone significantly reduced the risk of recurrent stroke in such patients. Accordingly, patients with IGT or diabetes, diagnosed by OGTT, may benefit from pioglitazone therapy in preventing the occurrence of ischemic stroke.

One limitation of the present study was that OGTT could not be performed in all ischemic stroke patients. However, this was because of physical disability or swallowing problems. OGTT is an important test for the diagnosis of disorders of glucose metabolism among patients with no history of diabetes.

In conclusion, the present study provides the first evidence to our knowledge that AGM is common in Japanese ischemic stroke patients with no history of diabetes. IGT and insulin resistance correlated significantly with pathogenic factor underlying the development of atherothrombotic infarction. Screening using OGTT was useful in identifying disorders of glucose metabolism in Japanese ischemic stroke patients with no history of diabetes.


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