Prevalence of Abnormal Glucose Tolerance Following a Transient Ischemic Attack or Ischemic Stroke

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Background: Despite current preventive therapies, patients with transient ischemic attack (TIA) and ischemic stroke remain at high risk for recurrent brain disease and cardiovascular events. In an effort to develop new therapies, abnormal glucose tolerance has recently been proposed as an interventional target. Among persons not otherwise known to be diabetic, impaired glucose tolerance (IGT) and diabetic glucose tolerance (DGT) are each associated with an increased risk for incident vascular disease, vascular disease mortality, and all-cause mortality. We conducted this study to determine if IGT and DGT are sufficiently common among patients with TIA and ischemic stroke to warrant therapeutic trials of antihyperglycemic agents.

Methods: Men and women older than 45 years were recruited from 3 hospitals in south central Connecticut. Eligibility criteria included a recent TIA or nondisabling ischemic stroke, no history of physician-diagnosed diabetes mellitus, and a fasting plasma glucose level less than 126 mg/dL (<7.0 mmol/L). After an overnight fast, subjects were admitted to a clinical research center for a standard 75-g oral glucose tolerance test. Impaired glucose tolerance was defined by a 2-hour plasma glucose value of 140 to 199 mg/dL (7.8-11.0 mmol/L) and DGT by a value of 200 mg/dL or greater (≥11.1 mmol/L).

Results: Between June 2000 and August 2003, we enrolled 98 eligible patients. The average time from TIA or stroke to measurement of glucose tolerance was 105 days (range, 24-180 days) and the median age was 71 years. Twenty-seven subjects (28%) had IGT and 24 (24%) had diabetes. In a forward stepwise logistic regression model, only a fasting plasma glucose level of 110 mg/dL or greater (≥6.1 mmol/L) and lower waist circumference were associated with an increased risk for IGT or DGT.

Conclusions: Impaired glucose tolerance and DGT are present in most persons with a recent TIA or ischemic stroke who have no history of diabetes and a fasting plasma glucose level less than 126 mg/dL (<7.0 mmol/L). Our findings bring new urgency to the initiation of research to examine the effectiveness of antihyperglycemic therapies among patients with cerebrovascular disease and abnormal glucose tolerance.

Arch Intern Med. 2005;165:227-233

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Financial Disclosure: Dr Inzucchi has received honoraria from and served as a consultant for Takeda Pharmaceuticals, which partly funded this study.

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and metabolic effects of IGT, persons with this condition develop diabetes, including DGT, at a much higher rate than persons with normal glucose tolerance. Diabetes, of course, is a well-established risk factor for atherosclerosis, stroke, and heart disease. Mechanisms by which diabetes leads to vascular disease are probably the same as those previously listed for IGT.11

Because of the adverse health consequences of IGT, several therapeutic trials have been conducted. In the US Diabetes Prevention Program, an intensive lifestyle intervention among persons with IGT reduced the incidence of diabetes by 58% compared with placebo. Similar findings were reported among obese northern European subjects who participated in the Finnish Diabetes Prevention Study. Pharmacologic interventions that prevent diabetes in high-risk individuals include thiazolidinediones, α-glucosidase inhibitors, and biguanides. The STOP–Noninsulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial investigators have reported that acarbose, an α-glucosidase inhibitor that specifically reduces postprandial hyperglycemia, reduced major cardiovascular events (coronary heart disease, cardiovascular death, congestive heart failure, transient ischemic attack [TIA], stroke, and peripheral vascular disease) by 49% compared with placebo among persons with IGT.16

Prevention studies have not focused on patients who have both a normal FPG level and DGT. They already have diabetes, so prevention of this end point is moot. Their risk for vascular disease, however, exceeds the risk among persons with IGT, and prevention of this end point would be very important. Persons with a normal FPG level and DGT usually do not require medications to achieve diabetes treatment goals and, therefore, would be candidates for enrollment in randomized, placebo-controlled clinical trials of antihyperglycemic medications to prevent vascular end points.

The foregoing epidemiologic and experimental data suggest that antihyperglycemic treatment of IGT and DGT may represent an important new therapy for patients with a history of TIA or stroke. Despite the use of antiplatelet agents and other proven therapies, patients with symptomatic cerebrovascular disease are still at high risk for recurrent cardiovascular events. On average, within 5 years of the initial event, 25% of patients will have a recurrent stroke, 10% will have a myocardial infarction, and 12% will die from one of these conditions. The potential impact of treatment for IGT and DGT will depend on the prevalence of these conditions, which is currently unknown. Both can only be detected after an oral glucose tolerance test (OGTT). In practice, physicians rarely perform an OGTT after stroke, and there has been no substantial research in this area. The aim of this study, therefore, was to ascertain the prevalence of IGT and DGT among a cohort of patients with symptomatic cerebrovascular disease.

## METHODS

### STUDY PARTICIPANTS

We studied men and women older than 45 years with no history of diabetes who were admitted to 1 of 3 participating hospitals between June 2000 and August 2003 for TIA or nondisabling ischemic stroke. All subjects were originally recruited for participation in studies on the prevalence of insulin resistance among patients with a recent TIA or ischemic stroke or the temporal trend in insulin resistance after ischemic stroke. A nondisabling stroke was recognized when a patient was able to communicate verbally, take 3 steps with or without the assistance of another person, and ride in a car. We enrolled only persons with nondisabling events to minimize the contribution of stroke-related inactivity to the measured insulin sensitivity. Patients were excluded if their cerebrovascular event was related to trauma, medical instrumentation, or embolism from an artificial heart valve. Patients were also excluded if they were taking oral corticosteroids, had irreversible medical conditions that were likely to affect short-term survival or ability to participate in the study protocol, or had an FPG value of 126 mg/dL or greater (≥7.0 mmol/L). Patients were identified by review of discharge logs from all participating hospitals and by weekly contact with stroke clinicians who volunteered to assist with surveillance. For patients discharged with International Classification of Diseases, Ninth Revision, Clinical Modification codes 433 through 436 (occlusion and stenosis precerebral arteries, occlusion cerebral arteries, transient cerebral ischemia, and acute but ill-defined cerebrovascular disease), we obtained permission for contact directly from personnel physicians. An effort was made to determine the eligibility of every patient with an appropriate discharge diagnosis, although complete records were not maintained to document reasons for exclusion of all nonenrolled potential subjects. This study was approved by the investigational review board at each participating hospital (Yale-New Haven Hospital, New Haven, Conn; Hospital of St Raphael, New Haven; and West Haven Veterans Administration Medical Center, West Haven, Conn), and all patients provided written informed consent.

### PATIENT ASSESSMENT

Patients who passed a telephone screening for eligibility were invited to the General Clinical Research Center of Yale-New Haven Hospital for an interview, physical examination, and OGTT (all completed on the same day). The interview comprised questions about medical conditions and current medications. The physical examination comprised anthropomorphic measures (weight, waist-hip circumference, and height) and blood pressure. Waist circumference was measured at the midpoint between the lower border of the rib cage and the iliac crest.

The OGTT was performed according to standard procedures modified to permit calculation of the Composite Insulin Sensitivity Index (Composite Index) described by Matsuda and DeFranzo. After baseline measures, subjects consumed 75 g of oral glucose. The Composite Index was calculated as the following:

\[
10000/[(FPG Value in Milligrams per Deciliter \times Fasting Plasma Insulin Value in Microunits per Milliliter) \times (Mean Plasma Glucose Concentration in Milligrams per Deciliter \times Mean Plasma Insulin Concentration in Microunits per Milliliter)]^{1/2}
\]

Mean plasma glucose and insulin values were obtained from measures made at 30, 60, 90, and 120 minutes after glucose administration. Higher index values indicate greater insulin sensitivity. As an additional measure of insulin sensitivity, we also calculated the Homeostasis Model Assessment of Insulin Resistance, which is estimated as the following:

\[
[(FPG Value in Millimoles per Liter) \times (Fasting Plasma Insulin Value in Microunits per Liter)]^{22.5}
\]
Higher values indicate greater insulin resistance. As a measure of β-cell function, we calculated the Homeostasis Model Assessment of β-cell function.21 Plasma glucose concentrations were measured by a glucose oxidation method (Glucose Analyzer 1; Beckman Instruments, Palo Alto, Calif). Plasma insulin was measured using a commercial radioimmunoassay kit (Linco Research, St Charles, Mo) that does not cross-react with human proinsulin.

STATISTICAL ANALYSIS

Baseline features of the study population were described by simple percentages. Hypertension was defined by self-report history and current use of an antihypertension drug, or by a blood pressure greater than 160/100 mm Hg. Myocardial infarction was defined by self-report of physician diagnosis of myocardial infarction for which the patient was hospitalized for more than 1 day. Carotid stenosis was based on carotid duplex ultrasonography obtained at the time of the cerebrovascular event. Atrial fibrillation was classified by an electrocardiogram obtained during the initial hospitalization for cerebrovascular symptoms or at the time of the glucose tolerance test. Obesity was defined according to standard criterion of a body mass index over 30 (calculated as weight in kilograms divided by the square of height in meters).26 Abdominal obesity was defined as a value greater than 102 cm for men and greater than 88 cm for women.27

Glucose tolerance was classified according to criteria established by the American Diabetes Association.28 Normal tolerance is defined by a plasma glucose value less than 140 mg/dL (<7.8 mmol/L) 2 hours after 75 g of oral glucose. Impaired glucose tolerance is defined by values of 140 mg/dL or greater (≥7.8 mmol/L) and less than 200 mg/dL (<11.1 mmol/L). Diabetes is defined by a value of 200 mg/dL or greater (≥11.1 mmol/L).

Unadjusted odds ratios were calculated for the occurrence of IGT or DGT (2-hour plasma glucose concentration of 140 mg/dL or greater [≥7.8 mmol/L]) among patients with and without specific clinical features. P values for these bivariate associations were calculated from the χ² statistic. An adjusted analysis was performed using a forward stepwise logistic regression model (with P values for entry and retention .10) that considered all subject features with a significant bivariate association with 2-hour plasma glucose concentration of 140 mg/dL or greater (≥7.8 mmol/L) (P<.10). All statistical analyses were performed using SAS statistical software (SAS version 8.0; SAS Institute Inc, Cary, NC).

RESULTS

Between June 2000 and August 2003, we enrolled 102 subjects. Four subjects were excluded because their FPG level exceeded 125 mg/dL (6.9 mmol/L), leaving 98 eligible subjects who were included in the analysis for this report. The average time from TIA or stroke to the OGTT was 105 days (range, 24-180 days).

The clinical features of the participants are given in Table 1. The median age was 71 years. The minority were female (39/98; 40%), 82 (84%) were white, 10 (10%) were African American, and 4 (4%) were Hispanic. The index event was a stroke (vs TIA) for 83 participants (85%), and 9 (10%) had carotid stenosis of more than 70%. The self-reported medical conditions were typical for patients with cerebrovascular disease. Eighteen participants (18%) were obese according to body mass in-

Table 1. Baseline Features for 98 Patients With a Recent TIA or Ischemic Stroke, a Fasting Plasma Glucose Level Less Than 126 mg/dL, and No History of Diabetes

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value±</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sociodemographic characteristic</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>71 (48-90)</td>
</tr>
<tr>
<td>Female sex</td>
<td>39 (40)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>82 (84)</td>
</tr>
<tr>
<td>African American</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Clinical characteristics‡</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>13 (13)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>61 (62)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>140 (101-195)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>80 (58-110)</td>
</tr>
<tr>
<td>Obesity</td>
<td>18 (18)</td>
</tr>
<tr>
<td>BMI</td>
<td>26 (18-44)</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>45 (46)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>98 (69-138)</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL</td>
<td>97.5 (76.0-124.0)</td>
</tr>
<tr>
<td>Homeostasis Model Assessment–insulin resistance</td>
<td>3.0 (0.5-10.4)</td>
</tr>
<tr>
<td>Homeostasis Model Assessment–β-cell</td>
<td>125 (19-808)</td>
</tr>
<tr>
<td>Insulin Sensitivity Index*</td>
<td>2.5 (0.4-10.2)</td>
</tr>
<tr>
<td>Neurological characteristic†</td>
<td></td>
</tr>
<tr>
<td>Index stroke (vs TIA)</td>
<td>83 (85)</td>
</tr>
<tr>
<td>Lacunar pathophysiology</td>
<td>22 (23)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Carotid stenosis &gt;70%‡</td>
<td>9 (10)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); DBP, diastolic blood pressure; SBP, systolic blood pressure; TIA, transient ischemic attack.

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.

*Data are given as median (range) or number (percentage) of patients.
†Definitions: myocardial infarction, self-report of hospitalization for more than 1 day for myocardial infarction; hypertension, self-report of physician diagnosis of hypertension and current use of hypertension medication or baseline blood pressure higher than 160/100 mm Hg; obesity, BMI greater than 30; abdominal obesity, greater than 102 cm for men and greater than 88 cm for women; Homeostasis Model Assessment, see “Methods” section; Composite Insulin Sensitivity Index, see “Methods” section; history of stroke, self-report of prior hospitalization for more than 1 day for stroke.
‡Eight subjects had missing data.
pressure; TIA, transient ischemic attack.

greater (2-hour plasma glucose concentration of 140 mg/dL or greater) was associated with an increased risk for stroke were each associated with an increased risk for higher FPG level, lower waist circumference, lower β-cell function (ie, lower value for the Homeostasis Model Assessment of β-cell function), and lacunar cause of stroke were each associated with an increased risk for 2-hour plasma glucose concentration of 140 mg/dL or greater (≥7.8 mmol/L). Of these, only FPG level and lower waist circumference entered the forward stepwise logistic regression analysis (adjusted odds ratio for glucose, 1.08 for each milligram-per-decilitter change [P = .002]; adjusted odds ratio for waist circumference, 0.95 for each centimeter change [P = .005]). When plasma glucose was defined as a dichotomous variable, the odds ratio for a value of 110 mg/dL or greater (≥6.1 mmol/L) was 5.55 (P = .01). The association between waist circumference and risk for 2-hour plasma glucose concentration of 140 mg/dL or greater (≥7.8 mmol/L) did not change after sequentially forcing potential confounding variables into the multivariable model, including hypertension, lacunar cause, sex, and age.

Our findings indicate that IGT or DGT are present in more than half of patients with a recent TIA or ischemic stroke who do not carry a prior diagnosis of diabetes and have an FPG level less than 126 mg/dL (<7.0 mmol/L). Not surprisingly, prevalence is increased among patients with IFG (ie, 110-125 mg/dL [6.1-6.9 mmol/L]), although reliance on FPG level alone would have missed 73% (37/51) of patients with an abnormal 2-hour plasma glucose concentration during the OGTT. In our population, several established risk factors for hyperglycemia (ie, older age, obesity, and increased waist circumference) were not predictive of abnormal glucose tolerance. In fact, a greater waist circumference appeared to be protective. Limited statistical power probably explains our failure to detect an effect of age.

The finding for waist circumference was not expected and was not explained by confounding variables. Potential explanations for the association include chance, bias, and biology. Chance is quantified by the bivariate P value (.05), which must be interpreted in consideration of the multiple risk factors we examined. Bias seems unlikely, although we cannot be certain that an unrecognized confounding variable did not affect the observed odds ratio. An additional source of bias may be patient selection. If larger patients at risk for stroke (ie, those with a larger waist circumference) are more commonly screened for diabetes than are smaller patients, then the larger patients in our cohort may represent a residual group with better glucose metabolism. To test this theory, we examined the prevalence of abnormal glucose tolerance according to quintile of waist circumference in our cohort. Our finding supported the theory that prevalence was similar in the first 4 quintiles but lowest in the fifth (data not shown). Biological factors may be at work if lower waist circumference in this older cohort indicates a lower lean body mass and, therefore, reduced capacity for glucose clearance into skeletal muscle. Had we adjusted the glucose dose for lean body mass, it is possible that waist circumference would no longer be associated with increased risk for IGT. Such adjustment, however, is not standard procedure.

To our knowledge, this is the first study of OGTT among patients with symptomatic cerebrovascular dis-
Impaired glucose tolerance was defined as 2-hour plasma glucose concentration between 140 and 199 mg/dL; diabetic glucose tolerance was defined as a 2-hour plasma glucose concentration of 200 mg/dL or greater. Studies are ordered by increasing magnitude of prevalence of diabetic glucose tolerance.

Evidence that IGT can be remediated also comes from research in nonstroke populations, but it is probably reasonable to assume that the findings are generalizable. Large clinical trials among patients with IGT have shown that glycemia can be improved, vascular risk factors can be attenuated, and diabetes can be prevented by lifestyle modification and treatment with metformin, troglitazone, and acarbose. Each of these trials, however, involved relatively young persons (mean ages, 50-55 years). New trials among older stroke patients with IGT could be designed to test simultaneously the effects of metabolic interventions for prevention of both diabetes and vascular disease.

The sampling and classification methods in our research may limit its generalizability and accuracy, but we believe these limitations are minor. We sampled only a portion of eligible hospitalized patients in 1 geographic area. Incomplete enrollment may have resulted in biased results if, for example, persons who consented to participate were healthier than persons who did not. The effect of this bias, we believe, would have been to underestimate the prevalence of IGT; healthier people who enrolled in the study, compared with those who did not enroll, may be more active, less obese, and, therefore, less likely to have IGT. The fact that we sampled patients from a geographic area probably has no significant effect on generalizability because population rates of impaired glucose metabolism and diabetes are similar across the United States. We classified subjects based on a single OGTT. The fact that we sampled patients from a geographic area probably has no significant effect on generalizability because population rates of impaired glucose metabolism and diabetes are similar across the United States. We classified subjects based on a single OGTT.

**Table 4. Prevalence of Impaired Glucose Tolerance and Diabetic Glucose Tolerance Among Selected cohorts of Persons Without Previously Diagnosed Diabetes**

<table>
<thead>
<tr>
<th>Publication Year</th>
<th>Population</th>
<th>No. of Subjects</th>
<th>Mean Age, y</th>
<th>&lt;140 mg/dL</th>
<th>140-199 mg/dL</th>
<th>≥200 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>Framingham offspring</td>
<td>2583</td>
<td>54</td>
<td>88</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>2001</td>
<td>Europeans</td>
<td>2178</td>
<td>53</td>
<td>87</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>2002</td>
<td>US community-dwelling adults with no clinical vascular disease</td>
<td>4014</td>
<td>73</td>
<td>54</td>
<td>32</td>
<td>14</td>
</tr>
<tr>
<td>Present study</td>
<td>Patients with a recent ischemic stroke</td>
<td>98</td>
<td>70</td>
<td>48</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>2002</td>
<td>Patients with a recent acute myocardial infarction</td>
<td>144</td>
<td>63</td>
<td>35</td>
<td>40</td>
<td>25</td>
</tr>
</tbody>
</table>

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.

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We believe that the OGTT findings we report indicate patients’ metabolic status from before their cerebrovascular event. The alternative explanation, that the findings indicate a metabolic response to cerebrovascular events, seems unlikely for 2 reasons. First, we performed the OGTT at least 3 weeks after the event, an interval that should be adequate to resolve inflammation and stress that may stimulate counterregulator hormones and worsened insulin resistance. Second, before their OGTT most of our subjects had resumed their usual level of physical activity.

Since the completion of this research, the American Diabetes Association has redefined IFG level to 100 to 125 mg/dL (5.6-6.9 mmol/L)\(^4\), levels below this indicate a normal glucose tolerance and above, diabetes. The prevalence of IGT among those with normal fasting glucose (n=54) and IFG (n=44) levels by the new definitions is 24% and 32%, respectively. The prevalence of diabetic glucose tolerance is 20% and 30%, respectively.

CONCLUSIONS

Impaired glucose tolerance and DGT are present in most patients with a recent TIA or ischemic stroke. Known risk factors for diabetes, such as IFG and obesity, are not sufficiently sensitive to be used alone as a screen for IGT and DGT. On the basis of our observational data and data linking abnormal glucose tolerance to vascular risk, we believe that metabolic therapy beyond the acute phase holds great promise for reducing morbidity and mortality after stroke. Initial clinical trials should enroll patients with documented abnormalities in glucose tolerance and test therapies that have been shown to be effective in disorders of glucose regulation, such as lifestyle modification, thiazolidinediones, metformin, and acarbose. The opportunities in this area are substantial, and the need for research is immediate.

Accepted for Publication: July 31, 2004.

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Funding/Support: This work was supported by grant MO1RR00125 from the National Institutes of Health/National Center for Research Resources/General Clinical Research Center program, Bethesda, Md; grant R01 DK-49230 from the National Institutes of Health; and by a grant from Takeda Pharmaceuticals North America, Inc, 208025, New Haven, CT 06520-8025 (walter.kernan@yale.edu).

Funding/Support: This work was supported by grant MO1RR00125 from the National Institutes of Health/National Center for Research Resources/General Clinical Research Center program, Bethesda, Md; grant R01 DK-49230 from the National Institutes of Health; and by a grant from Takeda Pharmaceuticals North America, Inc, 208025, New Haven, CT 06520-8025 (walter.kernan@yale.edu).

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