Impaired Glucose Tolerance and the Likelihood of Nonfatal Stroke and Myocardial Infarction

The Third National Health and Nutrition Examination Survey

Adnan I. Qureshi, MD; Wayne H. Giles, MD, MS; Janet B. Croft, PhD

Background and Purpose—Although diabetes mellitus (DM) is known to increase the risk of cardiovascular disease (CVD), the effect of impaired glucose tolerance (IGT) on the risk remains unclear. We determined whether IGT was associated with an increased likelihood for stroke and myocardial infarction in a nationally representative sample of US adults.

Methods—We evaluated the association between IGT (defined as a fasting glucose level of <140 mg/dL and a plasma glucose level of between 140 and 200 mg/dL 2 hours after administration of 75 grams of an oral glucose load) and DM (defined as the current use of insulin or an oral hypoglycemic medication, a fasting plasma glucose level of >140 mg/dL, or a plasma glucose level of >200 mg/dL 2 hours after administration of an oral glucose load) with a self-reported physician diagnosis of stroke and myocardial infarction in 6547 adults aged 40 to 74 years participating in the Third National Health and Nutrition Examination Survey. Multivariate logistic regression analyses were used to investigate these relationships.

Results—IGT and DM were observed in 1494 and 1532 adults, respectively. After adjustment for differences in age, gender, race/ethnicity, education, hypertension, cholesterol, body mass index, and cigarette smoking, IGT was not associated with stroke (odds ratio [OR], 0.9; 95% confidence interval [CI], 0.5 to 1.6) or myocardial infarction (OR, 1.1; 95% CI, 0.7 to 1.6). DM was associated with both stroke (OR, 1.6; 95% CI, 1.0 to 2.6) and myocardial infarction (OR, 1.9; 95% CI, 1.3 to 2.8).

Conclusions—In contrast to DM, IGT was not associated with an increased likelihood of prevalent nonfatal stroke or myocardial infarction. (Stroke. 1998;29:1329-1332.)

Key Words: diabetes mellitus ■ glucose tolerance ■ myocardial infarction ■ stroke

A n association between asymptomatic hyperglycemia and CVD was suggested in 1979 in a series of papers by the International Collaborative Group, including a collective analysis of 15 studies, that examined the relationship between IGT and CVD. More recently, it has been hypothesized that hyperglycemia below the level characteristic of DM may also be associated with an increased risk of CVD. However, most of the studies describing an association between IGT and CVD were performed in populations of European origin in which CVD was found to be more prevalent in subjects with IGT than in normoglycemic controls. Controversy exists regarding whether the relationship between IGT and CVD is causal or results from common antecedents. Because the prevalence of IGT and the rate of progression to DM varies widely among populations, we performed this study to analyze the independent association between IGT and nonfatal stroke and myocardial infarction in a nationally representative sample of US adults.

Subjects and Methods

The Centers for Disease Control and Prevention conducted the Third National Health and Nutrition Examination Survey between 1988 and 1994 to estimate the prevalence of common chronic conditions and associated risk factors among a nationally representative sample of the civilian, noninstitutionalized US population. NHANES III included a household interview; a medical examination at a mobile examination center; and phlebotomy to measure a number of hematologic factors, including glucose and cholesterol. The study sample included 6547 persons aged 40 to 74 years who participated in the NHANES III survey at the mobile examination center.

NHANES III participants who were examined at the mobile examination center and who were not current users of insulin or oral hypoglycemic medications underwent a 2-hour, 75-g oral glucose tolerance test. Examinees provided a fasting glucose blood specimen and then were administered an oral glucose challenge (Dextol-75) containing the equivalent of 75 g of glucose. A second specimen was drawn 2 hours after the first.

Participants were judged to have DM if they were current users of insulin or oral hypoglycemic medication, if they had a fasting plasma glucose concentration >140 mg/dL, or if they had a plasma glucose >200 mg/dL 2 hours after administration of the 75-gm glucose challenge. Participants were defined as having IGT if they had a fasting blood glucose <140 mg/dL and a plasma glucose between 140 and 200 mg/dL 2 hours after administration of the oral glucose challenge. Normal glucose tolerance (NGT) was defined as a fasting and 2-hour-postchallenge glucose value <140 mg/dL.

During the household interview participants were asked whether they had ever been told by a physician that they had suffered a stroke...
or heart attack; persons who answered in the affirmative were defined as having the condition. Potential confounders in the association between IGT and stroke and myocardial infarction included age, gender, race/ethnicity, education, hypertension, cholesterol, body mass index (weight [kg]/height [m²]), and cigarette smoking. Subjects were judged to be hypertensive if they were current users of antihypertensive medication or if they had an average blood pressure greater than or equal to 140/90 mm Hg. This average blood pressure was based on 3 blood pressure determinations obtained during the medical examination.

†See “Subjects and Methods” for definitions.

Values are means or percentages as indicated.

*Logistic regression model is adjusted for age, sex, education, race/ethnicity, hypertension, cholesterol, body mass index, and cigarette smoking.

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A total of 6547 adults aged 40 to 74 years either had DM or underwent the oral glucose tolerance test. A total of 1494 persons had IGT and 1532 had DM. Compared with persons with NGT, those with IGT or DM were older and had fewer years of education; had higher mean body mass index, cholesterol, and serum glucose values; and were more likely to be hypertensive (Table 1). The IGT and DM groups were less likely to be current smokers, while the NGT group was more likely to include men. The racial/ethnic composition of persons with IGT was similar to that for persons with NGT; by contrast, there was a higher proportion of Hispanics among the DM group than the NGT group.

The unadjusted prevalence of nonfatal stroke was higher among the IGT and DM groups than the NGT group (Table 2). However, the age-adjusted likelihood of stroke was similar for the IGT and the NGT groups (OR, 0.9; 95% CI, 0.5 to 1.7). By contrast, persons with DM had a significantly greater likelihood of nonfatal stroke than did persons with NGT (OR, 1.8; 95% CI, 1.1 to 3.0). Adjustment for other CVD risk factors did not substantially alter the risk estimates.

The prevalence of nonfatal myocardial infarction was also higher among the IGT and DM groups than the NGT group (Table 3). However, the age-adjusted likelihood of myocardial infarction for persons with IGT (OR, 1.1; 95% CI, 0.7 to 1.6) was similar to that for persons with NGT. In contrast, persons with DM had a significantly greater likelihood of myocardial infarction than did persons with NGT (OR, 2.0; 95% CI, 1.4 to 3.0). These relationships remained after adjusting for CVD risk factors.

**Discussion**

Since the introduction of IGT as a diagnostic category, there has been considerable interest in the possibility that IGT might be associated with an increased risk of CVD, similar to the relationship between diabetes mellitus and CVD. This study in a nationally representative sample of US adults was unable to demonstrate any association between IGT and nonfatal stroke and myocardial infarction after the adjustment for age and CVD risk factors.

A number of studies have investigated the incidence and prevalence of CVD in subjects with IGT. All of these studies used a standardized glucose tolerance test to evaluate hyperglycemic status, maintain uniform criteria, and avoid


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NGT* (n=3521)</th>
<th>IGT* (n=1494)</th>
<th>DM† (n=1532)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>52.3±6.6</td>
<td>56.6±8.2</td>
<td>59.8±8.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men, %</td>
<td>50.2±4.1</td>
<td>44.1±6.3</td>
<td>46.3±6.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Race/ethnicity, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic, white</td>
<td>87.3±8.5</td>
<td>87.5±8.2</td>
<td>82.1±7.8</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic, black</td>
<td>9.5±3.6</td>
<td>8.3±3.2</td>
<td>11.6±3.7</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>3.2±2.4</td>
<td>4.2±2.8</td>
<td>6.3±2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;12 years education, %</td>
<td>37.7±35.1</td>
<td>35.1±27.3</td>
<td>27.3±20.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.8±28.0</td>
<td>28.0±29.8</td>
<td>29.8±29.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>25.9±43.9</td>
<td>43.9±59.1</td>
<td>59.1±59.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol level, mg/dL</td>
<td>214.2±219.1</td>
<td>219.1±227.5</td>
<td>227.5±227.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum glucose level, mg/dL</td>
<td>92.5±95.7</td>
<td>95.7±149.5</td>
<td>149.5±149.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>27.2±21.6</td>
<td>21.6±19.8</td>
<td>19.8±19.8</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Values are means or percentages as indicated.

*See “Subjects and Methods” for definitions.


<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Stroke Prevalence, %</th>
<th>Age-Adjusted OR (95% CI)*</th>
<th>Multivariate Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGT†</td>
<td>3521</td>
<td>1.82</td>
<td>1.0 (referred)</td>
</tr>
<tr>
<td>IGT†</td>
<td>1494</td>
<td>2.17</td>
<td>0.9 (0.5–1.7)</td>
</tr>
<tr>
<td>DM†</td>
<td>1532</td>
<td>4.96</td>
<td>1.8 (1.1–3.0)</td>
</tr>
</tbody>
</table>

*Logistic regression model is adjusted for age, sex, education, race/ethnicity, hypertension, cholesterol, body mass index, and cigarette smoking.

†See “Subjects and Methods” for definitions.


<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Myocardial Infarction Prevalence, %</th>
<th>Age-Adjusted OR (95% CI)†</th>
<th>Multivariate Adjusted OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGT†</td>
<td>3521</td>
<td>3.54</td>
<td>1.0 (referred)</td>
</tr>
<tr>
<td>IGT†</td>
<td>1494</td>
<td>5.06</td>
<td>1.1 (0.7–1.6)</td>
</tr>
<tr>
<td>DM†</td>
<td>1532</td>
<td>10.68</td>
<td>2.0 (1.4–3.0)</td>
</tr>
</tbody>
</table>

*Logistic regression model is adjusted for age, sex, education, race/ethnicity, hypertension, cholesterol, body mass index, and cigarette smoking.

†See “Subjects and Methods” for definitions.
the biases associated with self-reported diagnosis. Although there are multiple studies of European origin, relatively few studies have been conducted in the United States. A cross-sectional study in Gothenburg found that only hypertension and heart failure were significantly associated with IGT; angina pectoris and stroke were not associated with IGT. A Colorado study found an increased prevalence of coronary heart disease in non-Hispanic white persons with IGT but no association in persons of Hispanic origin. The Paris Prospective Study evaluated glucose tolerance among 7038 men aged 43 to 54 with no previous cardiovascular disease. After 11 years of follow-up, persons with IGT at baseline evaluation had approximately twice the risk of CVD mortality as those with NGT. The Whitehall study, which followed 18 403 men aged 40 to 60 years for 18 to 20 years, also found that subjects with IGT had approximately twice the risk of CVD mortality as those with NGT. However, because 2% to 16% of persons with IGT progress into overt DM annually, the increased risk for CVD noted in prospective studies, especially those of long duration, is likely to be confounded by the undocumented development of DM during follow-up. This finding is supported by results from a Finnish study of elderly men aged 65 to 84 years, which reported no excess risk for CVD mortality in persons with IGT during a 5-year follow-up. In addition to study duration, another potential explanation for the lack of an association between IGT and CVD may be subject age. Our study population included elderly persons, a subgroup in which two other Finnish studies also failed to demonstrate any association between IGT and CVD.

The present study reported a higher prevalence of hypertension and a higher mean cholesterol level in those with IGT compared with those who had NGT. These findings are consistent with previous studies that have demonstrated an increased frequency of CVD risk factors in persons with IGT. The increased prevalence of CVD risk factors among persons with IGT may have confounded the association between IGT and CVD reported in other studies. This finding is further supported by our observation—before the adjustment for age and CVD risk factors—of an increased prevalence of both stroke and myocardial infarction in persons with IGT. This association disappeared after we adjusted for the confounding of age and other CVD risk factors.

This report is subject to a number of potential limitations. The definition of stroke and myocardial infarction used in the NHANES III survey was based on a self-reported physician diagnosis. O’Mahony et al validated the accuracy of assessing lifetime history of stroke in a random sample of 2000 persons aged 45 years and older using a mailed questionnaire. In that study, the accuracy of the participants’ self-reports of stroke was confirmed by a review of their medical records. The sensitivity of the question was 95%, and the specificity was 96%. Similarly high sensitivities (74% to 100%) and specificities (94% to 99%) have been reported for estimations of prevalent myocardial infarction. The questions on myocardial infarction and stroke in the NHANES III survey may in fact be more specific because not only was a physician diagnosis inquired, but the information was acquired during a personal interview rather than a mailed survey. Finally, the methodology used in this study did not permit us to evaluate the likelihood for fatal stroke and myocardial infarction. Fatal strokes and myocardial infarctions represent less than one third of all cardiovascular disease events. The exclusion of fatal events may have reduced our ability to detect significant differences; it is possible that IGT could be associated with only fatal cardiovascular disease events. However, previous studies have failed to demonstrate an association between diabetes mellitus and fatal stroke.

In conclusion, we were unable to demonstrate any association between IGT and either prevalent stroke or myocardial infarction in a nationally representative sample of US adults although the relationship between DM and cardiovascular disease was clearly demonstrable. Previous studies reporting such a relationship may not have fully taken into account many of the cardiovascular disease risk factors that may have confounded this association.

References


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