Fasting Plasma Glucose and Risk of Incident Ischemic Stroke or Transient Ischemic Attacks
A Prospective Cohort Study

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Background and Purpose—Diabetes and impaired fasting glucose are diagnosed based on an elevated plasma glucose level after an overnight fast. The diagnostic cutpoint of diabetes arises from the threshold for development of microvascular complications. Our aim was to examine the associations between clinical relevant categories of fasting glucose levels and the risk of incident ischemic stroke.

Methods—Patients with documented coronary heart disease who were screened for inclusion in a secondary prevention clinical trial (n=13,999) were followed-up. At baseline, medical histories were obtained and plasma glucose and lipids assessed at a central study laboratory. During a 6- to 8-year follow-up period 1037 cases were identified with ischemic cerebrovascular disease, of which, after reviewing hospital records with diagnoses of cerebrovascular disease, 576 cases were verified to have had ischemic stroke or transient ischemic attacks.

Results—Increasing fasting glucose level categories were positively associated with increasing age, male gender, body mass index, hypertension, total cholesterol, and triglycerides, and were inversely associated with high-density lipoprotein cholesterol and percent high-density lipoprotein of total cholesterol. In comparison with patients with fasting glucose levels of 90 to 99 mg/dL (n=3,706) who constitute the largest category, the odds ratios of ischemic cerebrovascular disease, adjusting for potential confounders, were 1.47 (95% CI, 1.07 to 2.02) for fasting glucose 80, 1.22 (0.98 to 1.52) for 80 to 89, 1.27 (1.02 to 1.60) for 100 to 109, 1.60 (1.26 to 2.03) for 110 to 125, 1.82 (1.33 to 2.49) for 126 to 140, and 2.82 (2.32 to 3.43) for >140 mg/dL. Similar J-shaped associations were observed in analysis excluding patients with known diagnosis of diabetes mellitus.

Conclusions—The association between fasting plasma glucose and incident ischemic cerebrovascular events in patients with pre-existing atherothrombotic disease is J-shaped. Rates increase for fasting plasma glucose levels >100 mg/dL and also for those with low fasting glucose levels. These findings may carry important implications for prevention strategies.

Key Words: diabetes mellitus ■ glucose ■ risk factors ■ stroke, ischemic

Cardiovascular and cerebrovascular complications are the leading causes of death and disability in patients with diabetes mellitus.1–6 Prospective epidemiological studies have confirmed an independent effect of diabetes on ischemic stroke (IS), with an increased relative risk ranging from 2-fold to 5-fold.2,7–10 Diagnosis of diabetes may be based on an elevated plasma glucose level after an overnight fast. By current criteria, diabetes was defined as fasting glucose levels ≥126 mg/dL (7.0 mmol/L).11 This diagnostic cutpoint is based mainly on the observation that levels ≥126 mg/dL usually reflect a serious metabolic abnormality that has been shown to be associated with microvascular complications.12 Impaired fasting glucose, a metabolic stage intermediate between normal glucose homeostasis and diabetes, was defined as fasting glucose levels 110 to 125 mg/dL (6.1 to 6.9 mmol/L). A recent follow-up report from the expert committee on the diagnosis and classification of diabetes mellitus recommended that impaired fasting glucose should be redefined as fasting glucose of 100 to 125 mg/dL (5.6 to 6.9 mmol/L).13

A large cohort of male and female patients with established coronary heart disease was screened for inclusion in a secondary prevention trial. The aim of the current study was to determine the relation between categories of fasting plasma glucose levels (<80, 80 to 89, 90 to 99, 100 to 109, 110 to 125, 126 to 140, and >140 mg/dL) and incident IS or transient ischemic attacks in this large prospective cohort.

Subjects and Methods

Study Participants
Patients with documented coronary heart disease were screened in 18 cardiac centers in Israel for inclusion in a placebo-controlled
secondary prevention randomized clinical trial assessing the effect of bezafibrate retard.14 Patients were screened between February 1990 and October 1992. Patients aged 45 to 74 years with evidence of myocardial infarction occurring ≥6 months but ≤5 years before enrollment or coronary insufficiency observed either at rest or during effort, as manifested by typical pain and dynamic electrocardiographic changes, or both, were eligible for screening. Coronary insufficiency episodes must have occurred between 6 months and 2 years before enrollment. In addition, specific serum lipid ranges were required because the study examined the efficacy of intervening to reduce serum triglycerides and increase high-density lipoprotein (HDL) cholesterol by a lipid-modifying drug. Known type 1 diabetes mellitus was excluded for screening. For the current analysis we also excluded patients with a history of previous stroke to assess the risk of first-ever stroke. The total number of patients in the present analysis was 13,999.

During the first physician visit, records were obtained on medical history, conventional risk factors, and medications used, and a complete physical examination was performed. Mortality data were obtained through January 1999 from the Israel Population Registry, with cause of death coded according to International Classification of Diseases, Ninth Revision (ICD-9) codes.

**Laboratory Methods**

Laboratory measurements were all performed at a central study laboratory (the Physiological and Hygiene Laboratory at the Wolfson Medical Center). Blood samples were taken after at least 12 hours of fasting. All analyses were performed with a Boehringer-Hitachi 704 random access analyzer using Boehringer diagnostic kits. Glucose concentrations were determined using an enzymatic colorimetric method (GOD/PAP).

**Assessment of Cerebrovascular Disease**

Patients included in the randomized clinical trial (Bezafibrate Infarction Prevention [BIP]; n = 3090) were routinely followed-up every 4 months, during which data on the occurrence of new cerebrovascular events were routinely obtained. For all other patients, we obtained computerized data files from hospitals participating in the study screening process up to the end of 1998. Hospitalizations with a diagnosis of cerebrovascular disease (ICD-9 codes 430 to 438 or code 38.1) were identified. We also matched the patients (based on national identification number and name) against a registry of the Clalit Health Services. This registry contains information on both Clalit-maintained hospitals participating in the screening process as well as several that did not participate. Patients were identified and attainable medical records and hospital discharge summaries were systematically reviewed. Data were collected on history, findings on neurological examination, brain computed tomography (CT), and ancillary examinations, as available, to verify the diagnosis and to determine stroke type. Patients, for whom the underlying cause of death was ischemic cerebrovascular disease (iCVD) by data obtained from the Israel Population Registry, were added as cases. A study stroke neurologist (D.T.) centrally reviewed all cases.

Our main outcome measures were, first, cases considered having any iCVD (n = 1037). This outcome measure included cases with ICD-9 codes of cerebrovascular disease other than hemorrhage or cases undergoing carotid endarterectomy, excluding cases considered to have had a nonvascular cause after chart review. Second, patients with IS/TIA (n = 576) were verified after review of medical records. For the remaining patients, medical records were not available for review or brain CT was not performed, so that type of event could not be definitely determined. Stroke was defined according to World Health Organization (WHO) criteria. Events resolving completely within <24 hours were diagnosed as a TIA. IS and intracerebral hemorrhage were differentiated by the results of brain CT performed at the acute stage. IS was diagnosed if the patient had an appropriate clinical event and had a brain CT that showed a compatible low-density lesion, or was normal, or had findings compatible with hemorrhagic conversion of a cerebral infarct.

**Statistical Analysis**

Data were analyzed with SPSS software version 11.0. Plasma glucose levels were categorized into 7 clinically relevant ranges. Associations of glucose categories and other risk factors, baseline characteristics, and medications were assessed by the ANOVA test for continuous variables and χ² test for categorical variables. Multivariate analysis of all iCVD and IS/TIA was performed with logistic regression models. Conventional risk factors for stroke were chosen for the final model on the basis of associations with plasma glucose categories. Rates of stroke did not differ between the arms of the BIP randomized clinical trial, assessing the effect of bezafibrate retard.14 Further, among other patients in the cohort, only a small fraction were using lipid-lowering medications at baseline (years 1990 to 1992), and exclusion of these patients did not effect the associations with stroke.14 Therefore, use of lipid-lowering drugs was not used as a covariate in the current analysis. A single measurement of glucose is subject to random fluctuation because of laboratory measurement and biological fluctuations. Because 6739 patients attended the second screening visit, at which another fasting glucose measurement was performed, we corrected for inter-variation of glucose measurements using the values of the first and second visits. The effect of calculating the regression dilution bias is to provide an estimate of the risk of iCVD risk associated with fasting glucose, correcting for regression to the mean.

**Results**

**Baseline Characteristics**

During the follow-up period 1037 cases of iCVD were identified, of which 576 cases were verified as having IS/TIA. Increasing categories of fasting glucose were associated with higher mean age, higher rates of males, known hypertension, and body mass index. Increasing categories of fasting glucose were also associated with higher mean serum levels of total cholesterol and triglycerides, lower levels of HDL cholesterol, and smaller percentage of HDL (Table 1). Patients with higher categories of fasting glucose overall tended to be treated more often with antihypertensive medications and less often with antiplatelets.

Fasting glucose levels in the range of 90 to 99 mg/dL constituted the largest category with approximately one-third of patients. Among patients without a diagnosis of diabetes mellitus, ∼7% of patients had levels <80 mg/dL and 8% had undiagnosed diabetes mellitus by current criteria. Impaired fasting glucose was present in 11% of patients by the criteria of 110 to 125 mg/dL (6.1 to 6.9 mmol/L), but in as high as 30% of patients by the new recommendations to redefine criteria to of 100 to 125 mg/dL (5.6 to 6.9 mmol/L).

Rates of all iCVD by baseline fasting glucose levels were as follows: 6.9% for <80 mg/dL, 6.0% for 80 to 89, 5.0% for 90 to 99, 6.4% for 100 to 109, 8.0% for 110 to 125, 9.3% for 126 to 140, and 13.6% for >140 mg/dL. Similar J-shaped relations were observed for the end-point of IS/TIA (Table 2). Distribution of subtypes of IS did not differ by glucose levels categorized into <90, 90 to 109, and ≥110 mg/dL (cardio-embolic 21%, 21%, and 22%, large vessel atherothrombosis 12%, 16%, and 11%, small vessel occlusive 7%, 9%, and 11%, and undetermined 60%, 56%, and 58%, respectively). In further analysis excluding patients with a known diagnosis of diabetes mellitus, similar trends were observed with plasma glucose (Table 3). The potential effect of conversion into diabetes during follow-up was assessed among the subgroup of 3090 patients included in the BIP randomized clinical trial,
Multivariable Analysis

In comparison with patients with fasting glucose levels of 90 to 99 mg/dL who constituted the largest category and exhibited the lowest risks, the relative odds of ICDV, adjusting for potential confounders, were 1.47 for fasting glucose <80, 1.22 for 80 to 89, 1.27 for 100 to 109, 1.60 for 110 to 125, 1.82 for 126 to 140, and up to 2.82 for >140 mg/dL (Figure). Relative odds in patients without a diagnosis of diabetes mellitus and for the end-point of IS/TIA exhibited similar trends (Tables 2 and 3). In comparison with patients with fasting glucose levels of 90 to 99 mg/dL, the relative odds of IS/TIA adjusting for potential confounders in patients without a diagnosis of diabetes mellitus were 1.48 for fasting glucose <80, 1.10 for 80 to 89, 1.22 for 100 to 109, 1.84 for 110 to 125, 1.46 for 126 to 140, and up to 2.05 for >140 mg/dL. The computed regression dilution factor for fasting glucose was 1.18. Adjusted relative odds corrected for the regression dilution factor are only slightly modified.

Discussion

Our study has shown that the association between fasting plasma glucose and incident ischemic cerebrovascular events in patients with pre-existing atherothrombotic disease is J-shaped. Rates increase for fasting plasma glucose levels >100 mg/dL, but also in those with low fasting glucose levels.

Clinical attention has focused on microvascular complications of diabetes mellitus. However, rates of myocardial

### TABLE 2. Adjusted Odds Ratios for Incident Ischemic Cerebrovascular Disease Among All Patients

<table>
<thead>
<tr>
<th>Fasting Plasma Glucose, mg/dL</th>
<th>All Ischemic Cerebrovascular Events</th>
<th>Ischemic Stroke/TIA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate (%)</td>
<td>Rate (%)</td>
</tr>
<tr>
<td></td>
<td>Model A</td>
<td>Model B</td>
</tr>
<tr>
<td>&lt;80</td>
<td>767</td>
<td>53 (6.9)</td>
</tr>
<tr>
<td>80–89</td>
<td>2737</td>
<td>164 (6.0)</td>
</tr>
<tr>
<td>90–99</td>
<td>3706</td>
<td>185 (5.0)</td>
</tr>
<tr>
<td>100–109</td>
<td>2275</td>
<td>146 (6.4)</td>
</tr>
<tr>
<td>110–125</td>
<td>1545</td>
<td>124 (8.0)</td>
</tr>
<tr>
<td>126–140</td>
<td>637</td>
<td>59 (9.3)</td>
</tr>
<tr>
<td>&gt;140</td>
<td>2332</td>
<td>318 (13.6)</td>
</tr>
<tr>
<td>All</td>
<td>13 999</td>
<td>1037 (7.4)</td>
</tr>
</tbody>
</table>

Model A indicates age-adjusted; Model B, adjusted for age, sex, body mass index, hypertension, triglycerides, % HDL, and antiplatelets, antihypertensives.
infarction and stroke in diabetic people are approximately twice the rates of microvascular events. In our study cohort of patients with pre-existing atherothrombotic disease, impaired fasting glucose was present in 11% by the criteria of 110 to 125 mg/dL, but in as high as 30% by the new recommended criteria to of 100 to 125 mg/dL. Those 30% were at increased risk of iCVD, supporting the recommended criteria.

Increasing categories of fasting glucose levels were positively associated with other components of the metabolic syndrome. Adjusting for these stroke risk factors and for use of antihypertensive medications and antiplatelets did not eliminate the associations observed. Accelerated development of atherosclerotic lesions of the large arteries occurs in the early, undiagnosed phase of type 2 diabetes. Newly detected type 2 diabetic patients exhibit a higher degree of early atherosclerosis than normal glucose-tolerant matched subjects, suggesting that hyperglycemia, together with a clustering of risk factors, may cause early atherosclerosis in the initial phases of diabetes. The clinical importance of easily detecting people at risk is related to strong evidence that prevention of weight gain and maintenance of physical activity levels in those who are at risk can prevent the development of abnormal fasting glucose and its progression of diabetes.

We have found an increased incidence of iCVD in patients with fasting glucose <90 mg/dL, and particularly <80 mg/dL. This is of special importance because among patients without a diagnosis of diabetes mellitus, approximately one-third of patients had levels <90 mg/dL, and ~7% had levels <80 mg/dL. There is a paucity of information about the association between low fasting glucose levels and vascular disease. Recently, low fasting glucose levels were found to be linked with a high risk of cardiovascular disease and all-cause mortality. As an important fuel of the brain, severely low fasting glucose may induce brain damage and dysfunction. There were only 2 patients with classic hypoglycemia with fasting glucose <50 mg/dL in the present study, and the exclusion of these participants did not alter the results. Hypoglycemia and rapid changes in plasma glucose have been shown to increase counter-regulatory hormones such as epinephrine and norepinephrine, which may induce vasoconstriction, platelet aggregation, and, thereby, ischemia.

Several potential sources of bias have been considered in our study. First, a common limitation to many observational studies is the absence of information concerning potential changes in fasting glucose levels and conversion into diabetes during follow-up. An analysis in a subgroup of our cohort that was followed-up as part of a randomized clinical trial revealed, however, similar trends with plasma glucose after excluding patients in whom diabetes developed during follow-up. Second, a majority of data regarding incident iCVD was obtained through medical record files from hospitals participating in this cohort. Patients with minor stroke events who were not admitted to a hospital, or those re-admitted to few hospitals not participating in this cohort, may have been missed. Incidence rates were, however, comparable in patients followed-up routinely as part of a randomized clinical trial to those in which data were obtained through medical records. Because complete medical records were not available in all cases, we assessed relative odds for both iCVD and for cases verified with IS/TIA, with similar associations identified. The 75-gram oral glucose tolerance

### Table 3. Adjusted Odds Ratios for Incident Ischemic Cerebrovascular Disease in Patients Without Diagnosed Diabetes Mellitus

<table>
<thead>
<tr>
<th>Glucose, mg/dL</th>
<th>Fasting Plasma Glucose, mg/dL</th>
<th>All Ischemic Cerebrovascular Events</th>
<th>Ischemic Stroke/TIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Rate (%)</td>
<td>Model A</td>
<td>Model B</td>
</tr>
<tr>
<td>&lt;80</td>
<td>470</td>
<td>1.56 (1.13–2.15)</td>
<td>1.61 (1.17–2.22)</td>
</tr>
<tr>
<td>80–90</td>
<td>2674</td>
<td>1.22 (0.97–1.52)</td>
<td>1.21 (0.97–1.52)</td>
</tr>
<tr>
<td>90–99</td>
<td>3577</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>100–109</td>
<td>2131</td>
<td>1.31 (1.04–1.65)</td>
<td>1.29 (1.02–1.63)</td>
</tr>
<tr>
<td>110–125</td>
<td>1245</td>
<td>1.69 (1.31–2.18)</td>
<td>1.67 (1.29–2.16)</td>
</tr>
<tr>
<td>126–140</td>
<td>347</td>
<td>1.40 (0.90–2.18)</td>
<td>1.36 (0.87–2.12)</td>
</tr>
<tr>
<td>&gt;140</td>
<td>512</td>
<td>2.61 (1.91–3.56)</td>
<td>2.49 (1.81–3.43)</td>
</tr>
<tr>
<td>All</td>
<td>11,226</td>
<td>697 (6.2)</td>
<td>384 (3.4)</td>
</tr>
</tbody>
</table>

Model A indicates age-adjusted; Model B, adjusted for age, sex, body mass index, hypertension, triglycerides, %HDL, antiplatelets, and antihypertensives.
test was not performed in the current study, nor were insulin levels measured. The fasting plasma glucose test is, however, recommended for use in the clinical setting, despite its inherent limitations, because it is easier and faster to perform, more convenient, and less expensive. Finally, the J-shaped association of fasting glucose in this study was found in a group of patients with pre-existing stable atherosclerotic disease, and caution should be used in generalization of our results to broader populations at lower risk for stroke.

References


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