Postchallenge Hyperglycemia in a National Sample of U.S. Adults With Type 2 Diabetes

Thomas P. Erlinger, MD, MPH¹
Frederick L. Brancati, MD, MHS¹,²

OBJECTIVE — Postchallenge hyperglycemia (PCH) is known to contribute to suboptimal glycemic control in adults with non–insulin-requiring type 2 diabetes. The objective of this study was to estimate the prevalence of PCH among individuals with diabetes.

RESEARCH DESIGN AND METHODS — We conducted a cross-sectional analysis of data from the Third National Health and Nutrition Examination Survey (1988–1994) in adults aged 40–74 years with diabetes who were not using insulin (i.e., they used oral hypoglycemics or received no pharmacological therapy). Each respondent underwent a standard 75-g oral glucose tolerance test. PCH was defined as a 2-h glucose level ≥200 mg/dl.

RESULTS — Overall, PCH was present in 74% of those with diagnosed diabetes. Although it was present in virtually all (99%) of the diabetic adults under suboptimal glycemic control (HbA₁c ≥7.0%), PCH was also common (39%) among those under optimal control (HbA₁c <7.0%). Likewise, among sulfonylurea users, PCH was present in 99% of those under suboptimal control and in 63% of those under good control. Similar patterns were observed in those with undiagnosed diabetes. Isolated PCH (2-h glucose ≥200 mg/dl and fasting glucose <126 mg/dl) was present in 9.8% of the adults with diagnosed diabetes.

CONCLUSIONS — These data suggest that PCH is common among diabetic adults in the U.S., even in the setting of “optimal” glycemic control and sulfonylurea use. Interventions designed to lower postprandial glucose excursions may help improve overall glycemic control in the general population of U.S. adults with diabetes.

Hyperglycemia is a major modifiable risk factor for morbidity and mortality in diabetes (1,2). Improvements in glycemic control have been shown to reduce the risk of these complications in type 1 and type 2 diabetes (3,4). PCH contributes to poor glycemic control, and agents that modify PCH reduce HbA₁c levels (5,6). PCH also appears to be an independent risk factor for the development of atherosclerosis and fatal coronary heart disease (7,8). Moreover, recent findings suggest that with regard to deaths from all causes and cardiovascular disease, 2-h glucose is a better predictor than fasting blood glucose (9).

Thus, PCH might represent an attractive target in the primary care of adults with diabetes. However, PCH appears to receive relatively little attention in primary care. Most treatment guidelines recommend monitoring of HbA₁c and/or fasting glucose levels (10). Patients who self-monitor overwhelmingly report monitoring before meals (11).

One possible explanation for the lack of attention paid to PCH is uncertainty about its prevalence in adults with previously diagnosed diabetes. However, if common, it would be a logical target for interventions to improve glycemic control in the U.S. We therefore analyzed data from a nationally representative cohort of diabetic adults in the U.S. who participated in the Third National Health and Nutrition Examination Survey (NHANES III) and underwent an oral glucose tolerance test (OGTT). We hypothesized that PCH would be common, especially in those with suboptimal glycemic control. We paid particular attention to the influence of sulfonylureas, the most commonly used class of oral hypoglycemic agents.

RESEARCH DESIGN AND METHODS

Data source
We used data from NHANES III, which was conducted between October 1988 and October 1994 by the National Center for Health Statistics in two equal 3-year phases (1988–1991 and 1991–1994). A stratified multistage sample design was used to select a study sample representative of the entire civilian noninstitutionalized U.S. population. The survey included a physical examination, laboratory tests, and questionnaires on health and nutrition-related topics. A detailed description of the survey design, response rates, and procedures for blood collection and processing have been previously published elsewhere (12,13).

Study sample selection
A total of 18,825 adults who were 20 years of age and older completed the household interview, in which information was obtained about demographic characteristics, race, and medical history.
of diabetes. Participants were defined as having previously diagnosed diabetes if they answered “yes” to the following question: “Have you ever been told by a doctor that you have diabetes or sugar diabetes?” Of the 1,605 individuals over age 20 years with a history of physician-diagnosed diabetes, 105 women were diagnosed only during pregnancy and were excluded from this analysis. A subsample aged 40–74 years was selected to receive an OGTT. We excluded those who did not fast 9–24 h before the OGTT and those who were missing data with respect to relevant glycemic indexes. In the end, 218 individuals with a history of previously diagnosed type 2 diabetes were included in our analyses. Of these, 134 used oral hypoglycemic agents and 84 reported receiving nonpharmacological management for their diabetes. Cases of previously undiagnosed diabetes were identified according to American Diabetes Association diagnostic criteria: either fasting plasma glucose (FPG) ≥126 mg/dl or 2-h glucose ≥200 mg/dl (14).

Data collection
Procedures of physical examination, blood collection, and processing have been described in detail elsewhere (13). HbA1c was measured at the University of Missouri Diabetes Diagnostic Laboratory using high-performance liquid chromatography. Plasma glucose was measured using a modified hexokinase enzymatic method. BMI was calculated as the weight in kilograms divided by the square of height in meters. Current smokers were those who gave a history of current smoking or had a serum cotinine level >10 ng/ml. Race and ethnicity were determined by self-report. Blood pressure was the average of measurements obtained at the household interview (maximum of three measurements) and the mobile examination center (maximum of three measurements). Serum cholesterol was measured enzymatically (Hitachi 704 analyzer; Boehringer Mannheim).

For the OGTT, a 75-g glucose-equivalent oral glucose (Dextol or Trutol) test was given to a morning subsample of participants. Data were used from those participants who were fasting from 9 to 24 h and who had plasma collected after 120 min ± 15 min. Insulin users were excluded from the morning subsample. Individuals with a history of diabetes who were using oral hypoglycemic agents were asked not to take them on the morning of the test.

Guidelines from the American Diabetes Association for the management of diabetes were followed to estimate the proportion of adults with diabetes under optimal, fair, and poor glycemic control (HbA1c <7.0, 7.0–8.0, and >8.0%, respectively) (15), by level of fasting (<126, 126–140, and 140 mg/dl, respectively) and 2-h glucose levels (<140, 140–200, and 200 mg/dl, respectively) (14). Isolated PCH was considered present if 2-h glucose was ≥200 mg/dl and fasting glucose was <126 mg/dl.

Analysis
We used sample weights in calculating means and proportions to account for the complex, stratified probability sampling design and to make estimates that were representative of the U.S. population. To test for differences between adults with diabetes who were treated with oral agents and those not receiving pharmacological therapy with respect to baseline characteristics, we used analysis of variance for continuous variables (age, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL cholesterol, BMI, FPG, 2-h postchallenge plasma glucose, and HbA1c) and logistic regression for dichotomous outcomes (sex and smoking). Logistic regression was used to test for differences in the proportion of diabetes adults with hyperglycemia who were taking oral agents and those not taking oral agents who had an HbA1c level <7.0 and were adjusted for age, race, sex, BMI, and smoking status. Linear correlation between fasting and 2-h glucose levels was determined by taking the square root of the variance from the weighted linear regression model that incorporated 2-h glucose as a function of FPG.

As a subsidiary analysis, we calculated the prevalence of fasting and 2-h hyperglycemia in individuals with previously undiagnosed diabetes in order to confirm patterns observed in previously diagnosed individuals. All analyses were conducted using survey commands in STATA statistical software version 6.0 (College Station, TX).

RESULTS
Baseline characteristics
Table 1 shows selected characteristics of U.S. adults with diabetes who were not using insulin. Compared with those taking oral hypoglycemic agents, diabetic adults on no pharmacological therapy were slightly older, and a greater proportion of that group was female and non-Hispanic white. Additionally, those not treated had a lower BMI than those receiving treatment. As expected, untreated adults with diabetes were generally under better glycemic control than treated individuals and had lower fasting and 2-h plasma glucose levels.

Prevalence of hyperglycemia
PCH was common in this national sample of adults with previously diagnosed diabetes; its prevalence rising from 39% in those under “optimal” control (HbA1c <7.0%) to >99% in those under “fair” and “poor” control (HbA1c 7.0–7.9 and 8.0%, respectively) (Table 2). This corresponds to mean 2-h glucose levels of 325 and 402 mg/dl in those with fair and poor control, respectively. As expected, mean levels of fasting glucose and the prevalence of fasting hyperglycemia (FPG 140 mg/dl) also rose across categories of HbA1c. Nonetheless, isolated PCH (FPG <126 mg/dl and 2-h glucose 200 mg/dl) was present in 9.8% of the adults with diagnosed diabetes (data not shown).

Postprandial hyperglycemia and medication use
The use of oral antidiabetic medication (sulfonylureas) was not associated with lesser degrees of hyperglycemia (Fig. 1). On the contrary, both fasting and PCH were equally or more common in those taking sulfonylureas than in those not taking them. This difference reached statistical significance among those under optimal control (P <0.001).

Correlation between fasting and 2-h glucose levels
To investigate the correlation between fasting and 2-h glucose levels in adults with diagnosed diabetes, we plotted mean plasma glucose levels against HbA1c levels (Fig. 2). As expected, there were strong associations of HbA1c with FPG (β = 0.024, 95% CI 0.021–0.027) and 2-h glucose (0.012, 0.011–0.013). Consequently, the correlation between FPG and 2-h glucose was high (r² = 0.72, P < 0.001).
Postprandial hyperglycemia in adults with diabetes

CONCLUSIONS

These data demonstrate a high prevalence of PCH among adults with previously diagnosed diabetes, even among those being treated with oral hypoglycemic agents. In fact, even among individuals under optimal glycemic control with oral agents, almost two-thirds have 2-h postchallenge hyperglycemia. Moreover, ~10% of adults with previously diagnosed diabetes who have an FPG <126 mg/dl have PCH.

The main strength of this study is that it draws on a nationally representative sample and is therefore generalizable to the U.S. population. Nevertheless, several limitations should be kept in mind. Because of the cross-sectional study design, we are not able to determine cause-and-effect relationships, especially in regard to medication use. In particular, we cannot exclude the possibility that preferential prescription of sulfonylureas to adults with PCH might explain the observed associations between PCH and sulfonylurea use. Second, because our study was limited to diabetic individuals aged 40–74 years who were not taking insulin, we cannot comment on the prevalence of PCH among younger or older age groups. However, diabetes prevalence has sharply increased in younger and older age groups; thus, our estimates of the total number of diabetic individuals with PCH are likely conservative (16). Third, our estimates of elevated 2-h plasma glucose levels could be artificially inflated because of skipped morning doses of oral hypoglycemic agents before the glucose challenge in diagnosed diabetic patients. However, we observed similar patterns in FPG levels, which are not likely to be affected by skipped medication doses. Treatment with oral hypoglycemic agents could theoretically result in an underestimation of the prevalence of PCH. However, the prevalence of PCH is nearly ubiquitous, except in individuals with an

Table 1—Selected characteristics of non–insulin-using diabetic adults in the U.S. aged 40–74 years by oral agent status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>On oral agents (sample n = 134, weighted N = 2,090,271)</th>
<th>Not on oral agents (sample n = 84, weighted N = 1,571,692)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.8 (1.3)</td>
<td>60.1 (1.2)</td>
<td>0.45</td>
</tr>
<tr>
<td>Women (%)</td>
<td>40.3 (3.0)</td>
<td>47.3 (8.3)</td>
<td>0.49</td>
</tr>
<tr>
<td>Race-ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>75.7 (4.3)</td>
<td>84.8 (3.7)</td>
<td>0.12</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>11.8 (2.5)</td>
<td>8.2 (2.5)</td>
<td>0.12</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8.1 (1.8)</td>
<td>7.0 (2.0)</td>
<td>0.12</td>
</tr>
<tr>
<td>Other</td>
<td>4.4 (2.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>134.2 (2.1)</td>
<td>133.4 (2.6)</td>
<td>0.80</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>76.2 (1.1)</td>
<td>73.6 (1.4)</td>
<td>0.14</td>
</tr>
<tr>
<td>Total cholesterol (mmol/dl)</td>
<td>225.2 (5.8)</td>
<td>233.5 (7.1)</td>
<td>0.41</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/dl)</td>
<td>44.3 (3.5)</td>
<td>47.3 (2.0)</td>
<td>0.46</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.1 (0.6)</td>
<td>29.1 (0.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>17.7 (4.6)</td>
<td>41.2 (10.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>189.2 (9.2)</td>
<td>148.4 (12.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>2-h plasma glucose (mg/dl)</td>
<td>333.1 (15.4)</td>
<td>244.1 (27.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.0 (0.2)</td>
<td>6.6 (0.3)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Values are means (SEM) or proportions (SEM), weighted to reflect the U.S. population.

Table 2—Distribution of FPG and 2-h postchallenge glucose by HbA1c levels in U.S. adults with diagnosed diabetes

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>(Weighted N)</th>
<th>Mean</th>
<th>&lt;126</th>
<th>126–140</th>
<th>≥140</th>
<th>Mean</th>
<th>&lt;126</th>
<th>140–200</th>
<th>≥200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>218 (3,661,964)</td>
<td>172.5 (6.8)</td>
<td>28.1% [n = 70]</td>
<td>14.9% [n = 27]</td>
<td>57.0% [n = 121]</td>
<td>294.7 (14.6)</td>
<td>16.1% [n = 26]</td>
<td>10.4% [n = 32]</td>
<td>73.5% [n = 160]</td>
</tr>
<tr>
<td>&lt;7</td>
<td>104 (1,572,903)</td>
<td>118.9 (3.0)</td>
<td>59.9% [n = 66]</td>
<td>27.4% [n = 19]</td>
<td>12.7% [n = 19]</td>
<td>184.7 (10.1)</td>
<td>36.8% [n = 24]</td>
<td>24.2% [n = 32]</td>
<td>39.0% [n = 48]</td>
</tr>
<tr>
<td>7–7.9</td>
<td>41 (744,515)</td>
<td>169.4 (6.8)</td>
<td>10.2% [n = 3]</td>
<td>10.2% [n = 7]</td>
<td>79.5% [n = 31]</td>
<td>325.1 (11.5)</td>
<td>0.01% [n = 1]</td>
<td>0% [n = 0]</td>
<td>99.9% [n = 40]</td>
</tr>
<tr>
<td>≥8</td>
<td>73 (1,344,546)</td>
<td>235.9 (8.6)</td>
<td>0.7% [n = 1]</td>
<td>3.0% [n = 1]</td>
<td>96.4% [n = 72]</td>
<td>402.4 (12.8)</td>
<td>0.7% [n = 1]</td>
<td>0% [n = 0]</td>
<td>99.3% [n = 73]</td>
</tr>
</tbody>
</table>

Results shown as weighted proportions and means (SEM). Numbers in brackets indicate the number of individuals from the NHANES III sample on which these estimates are based.
HbA\textsubscript{1c} level $<7\%$. Therefore, this is the group for which these comments are relevant. Consequently, our estimates are potentially conservative in this group. Finally, although the prevalence of PCH in this study was high among individuals with diabetes, post–mixed-meal glucose levels would be expected to be lower than 2-h glucose levels (17). Nevertheless, 2-h glucose levels above normal but $>200$ mg/dl are still associated with an increased risk of mortality (9). Current recommendations for postmeal glycemic control are 100–150 mg/dl (15).

Previous analyses from NHANES III have shown a similar magnitude of poor glycemic control among diagnosed diabetic patients with respect to FPG levels (18). Data from NHANES III and other populations have also documented a high prevalence of PCH in adults with previously undiagnosed diabetes, identified based on elevations in FPG or HbA\textsubscript{1c} (5,12,19–22). However, to our knowledge, no previous studies have examined the prevalence of elevated postchallenge glucose levels among adults with diabetes.

The loss of early phase insulin secretion may be a key factor in postprandial hyperglycemia as well (23,24). Additionally, insulin resistance within muscles and impaired suppression of hepatic glucose production may also contribute to postprandial hyperglycemia (25). PCH has been shown to increase the risk of microvascular and macrovascular complications in individuals with diabetes (7,26), and the increased prevalence of PCH demonstrated in this study suggests that it could be an important target for interventions aimed at reducing glycemia among individuals with diabetes.

The differences between the prevalence of PCH among those treated with oral agents and those not treated with oral agents are likely due to more severe hyperglycemia among treated individuals. However, because the data in this study were collected when sulfonylureas were the only oral hypoglycemic agents available for the treatment of type 2 diabetes (1988–1994), it is not clear whether newer agents designed to specifically reduce PCH would reduce the prevalence beyond that achieved with sulfonylureas, given the same level of long-term glycemic control.

It would be impractical for most providers seeking to optimize glycemic control among adults with type 2 diabetes to routinely order OGTTs. One alternative would be for primary care providers to recommend the monitoring of postprandial glucose in addition to fasting or preprandial. Another alternative would be to rely on FPG as an indirect indicator of PCH, as is currently the standard of practice, because the two are highly correlated.

Such correlation raises an important question: Does it make sense to focus on PCH per se, when it is so often accompanied by fasting hyperglycemia? Three lines of reasoning suggest a tentative answer of “yes.” First, PCH is a strong predictor of cardiovascular disease, even in the absence of fasting hyperglycemia (7). Second, specific pharmacotherapy is available to modify PCH preferentially. Third, compared with sulfonylureas, such agents offer a theoretical advantage in terms of hypoglycemic risk, in so far as they modify glucose peaks but leave troughs unaffected (27). Long-term studies are needed to determine whether agents that specifically target PCH reduce the risk of vascular complications among diabetic patients compared with other agents. In the meantime, this study underscores that PCH is common enough to
Postprandial hyperglycemia in adults with diabetes

warrant clinical attention, even in the setting of reasonably good glycemic control.

References


