Utility of 2-Hour Postchallenge Glucose in Predicting Incident Diabetes in Older Adults with Normal Fasting Glucose: 9-Year Follow-up of the Cardiovascular Health Study

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Abstract

• **Objective:** To describe the value of measuring 2-hour postchallenge glucose (2HG) levels for predicting the development of diabetes mellitus (DM) among adults aged 65 years and older with normal fasting glucose (FG).

• **Design:** Prospective cohort study with baseline and annual clinic visits.

• **Setting and participants:** 2213 participants with normal FG (< 100 mg/dL) at baseline from 4 communities throughout the United States comprising the Cardiovascular Health Study.

• **Measurements:** New-onset DM was defined as a FG level of 126 mg/dL or higher or starting DM medication. We calculated DM incidence rates during 9 years of follow-up overall and stratified by baseline 2HG level (< 140, 140–199, and ≥ 200 mg/dL).

• **Results:** Thirty-six participants (1.6%) developed DM during a mean follow-up of 7.7 years (overall crude incidence rate of 2.1 cases per 1000 person-years). DM incidence rates according to baseline 2HG categories were 1.6 (< 140 mg/dL), 2.3 (140–199 mg/dL), and 9.8 (≥ 200 mg/dL) per 1000 person-years. After adjusting for age, sex, and race, individuals with baseline 2HG of 200 mg/dL or higher were 7 times more likely to develop DM compared with those with baseline 2HG below 140 mg/dL (hazard ratio [HR], 7.0 [95% confidence interval (CI), 2.9–16.9]). These risks changed little after adjusting for FG and body mass index (HR, 6.3 [95% CI, 2.6–15.4]). Among those with baseline 2HG of 200 mg/dL or higher, all new DM cases occurred among participants with at least 1 traditional DM risk factor.

• **Conclusion:** Although 2HG is predictive of DM, the overall rate of DM in older adults with normal FG is low.
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Methods

Study Cohort

The CHS is a prospective study of coronary heart disease and stroke in adults aged 65 years and older [15]. In 1989, 5201 subjects constituting the original cohort were enrolled from 4 communities: Allegheny County, PA; Sacramento County, CA; Washington County, MD; and Forsyth County, NC [16]. The cohort was scheduled to have annual clinic visits for 9 years through 1999. An African American cohort consisting of 687 individuals was recruited subsequent to the original cohort. The African American cohort is not included in this analysis because baseline measures of 2HG were not obtained for these participants. This analysis includes only those participants in the original cohort who at baseline examination had normal FG (< 100 mg/dL), had an oral glucose tolerance test in which 2HG values were obtained, and were not taking diabetic medications. The CHS was conducted with full approval by the institutional review boards at the respective sites. Each participant provided informed consent consistent with Declaration of Helsinki guidelines.

Data

Participants were asked to fast overnight for routine serum chemistry tests (including measurement of FG, 2HG, and insulin level) and measurement of plasma lipids and coagulation factors. Fasting participants not receiving medications for DM were administered a 75-g oral glucose tolerance test, and a 2HG sample was obtained consistent with established standards [17]. Less than 4% of those eligible for the tolerance test did not take the test. Additional information collected at baseline included routine demographic (age, sex, race [Caucasian versus other]), anthropometric (body mass index [BMI], waist-hip ratio), and clinical (systolic and diastolic blood pressure) data. Annual medication inventories were administered, additional FG measures were obtained at the 3- and 7-year follow-ups, and an additional 2HG measurement was obtained at 7-year follow-up.

Analysis

Normal FG at baseline was defined as less than 100 mg/dL consistent with the current ADA definition [3]. Participants with normal FG were categorized by 2HG values as normal (< 140 mg/dL), impaired glucose tolerance (IGT) (140–199 mg/dL), and DM (≥ 200 mg/dL) according to WHO criteria [2]. Baseline characteristics among participants classified as IGT and DM were compared with characteristics of those with normal 2HG values. One-way analysis of variance was used for comparison of continuous variables. Fisher’s exact and chi-square tests were used for comparison of categorical variables.

Incident DM was defined as FG of 126 mg/dL or higher on year 3 or 7 follow-up visit or the initiation of oral hypoglycemic agents or insulin therapy as reported on annual medication inventories. Person-year incidence rates of DM were calculated and stratified by 2HG groups. The total number of events in a group and the probability of an event (proportion of person-years of follow-up) were compared between the IGT, DM, and normal groups. Hazard ratios (HRs) were derived from Cox proportional hazard regression analyses and used to estimate the relative risk of DM among the 2 groups with elevated baseline 2HG measures (140–199 and ≥ 200 mg/dL) compared with the group with normal 2HG measures (< 140 mg/dL). Analyses included adjustments for age, sex, race, FG, and BMI. One-way interaction terms were introduced to evaluate the presence of 2HG effect modification by sex, race, and continuous measures of FG, age, and BMI. Similar multivariate regression analyses were performed using the interquartile range of baseline 2HG instead of the WHO 2HG categorization.

Results

Among 4551 CHS participants in the original cohort who were not receiving antidiabetic medication and who had both FG and 2HG tests at baseline, 2213 (48.6%) had normal FG. Of these participants, nearly one third had elevated 2HG: 580 (26.2%) with levels from 140 to 199 mg/dL and 94 (4.2%) with levels over 200 mg/dL. Participants in the elevated 2HG groups were older, were more likely to be female, and had higher BMI and waist-hip ratio measures than participants in the normal 2HG group (Table 1). In addition, they had significantly higher levels of cardiovascular disease risk factors, including higher levels of FG, fasting and postchallenge insulin, total cholesterol, triglycerides, fibrinogen, and systolic blood pressure and lower high-density lipoprotein levels.

At 9-year follow-up, 1134 (51.2%) participants with normal FG at baseline participated in the annual clinic visit: 439 (19.8%) participated in home or telephone visits, 565 (25.5%) had died, and 75 (3.4%) were unavailable. Among the 2213 participants, 36 (1.6%) developed DM during an average of 7.7 years of follow-up (median follow-up, 8.9 years). Of these 36 cases, 16 were defined as having DM by a FG level of 126 mg/dL or higher alone and 20 by use of antidiabetic medication, with or without a FG of 126 mg/dL or higher. This corresponded to an overall unadjusted incidence rate of 2.1 cases per 1000 person-years. Of the 36 cases, 19 (1.2%) occurred in the normal group, 10 (1.7%) in the IGT group, and 7 (7.5%) in the DM group, corresponding to unadjusted incidence rates of 1.6, 2.3, and 9.8 per 1000 person-years, respectively.

Individuals with baseline 2HG values of 200 mg/dL or higher were 7 times (HR, 7.0 [95% confidence interval [CI], 2.9–16.9]) more likely to develop DM compared with those with baseline 2HG values below 140 mg/dL when adjusting...
for age, sex, and race (Table 2). These risks changed little after additionally adjusting for baseline FG and BMI (HR, 6.3 [95% CI, 2.6–15.4]). Participants with baseline IGT were not at increased risk for incident DM compared with those with a normal 2HG level (HR, 1.5 [95% CI, 0.72–3.3]). The corresponding HR based upon the interquartile range 2HG increase (48 mg/dL) was 2.3 (95% CI, 1.6–3.2) in the model adjusting for age, sex, and race, and was 2.2 (95% CI, 1.5–3.2) in the model adjusting for age, sex, race, FG, and BMI. No significant 2HG effect modification for risks of DM was seen for FG, age, sex, race, or BMI (all P values for interactions ≥0.1).

Among participants with normal FG and DM-level 2HG at baseline (n = 94), those who developed DM (n = 7) were more likely to be non-Caucasian (P = 0.021), obese (BMI ≥30; P = 0.005), and have systolic blood pressure above 140 mm Hg (P = 0.061) than those who did not develop DM. Those who developed DM had at least 1 traditional DM risk factor: elevated systolic pressure alone (n = 1); non-Caucasian and either obesity or elevated systolic blood pressure (n = 3); all 3 risk factors (n = 3). Other baseline characteristics were not associated with DM onset among those with baseline 2HG of 200 mg/dL or higher.

**Discussion**

In this longitudinal study of older, primarily non-Hispanic Caucasian adults with normal FG, only a small proportion of the cohort (1.6%) developed DM as defined by FG criteria or initiation of diabetic medications during the nearly 9 years of follow-up. Within this group, baseline 2HG values of 200 mg/dL or higher was a stronger predictor of DM than normal 2HG. Participants with baseline 2HG of 200 mg/dL or higher were over 6 times more likely to develop DM than those with normal 2HG values. While the overall number of incident DM cases was small, nearly 20% of new-onset DM occurred among individuals with baseline 2HG of 200 mg/dL or higher.

In addition to the overall low incidence of DM observed in our study, we found that those individuals with elevated
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Table 2. 9-Year Diabetes Incidence Rates and Relative Hazards in Individuals with Normal Fasting Glucose

<table>
<thead>
<tr>
<th>Baseline 2-Hour Glucose</th>
<th>Incident diabetes, n</th>
<th>Follow-up, person-years</th>
<th>Unadjusted rate, no./1000 person-years</th>
<th>Adjusted RH (95% CI)* (reference) (0.72–3.3)</th>
<th>Adjusted RH (95% CI)† (reference) (0.61–2.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 140 mg/dL (n = 1539)</td>
<td>19</td>
<td>12,073</td>
<td>1.6</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>140–199 mg/dL (n = 580)</td>
<td>10</td>
<td>4289</td>
<td>2.3</td>
<td>1.5 (0.72–3.3)</td>
<td>1.3 (0.61–2.9)</td>
</tr>
<tr>
<td>≥ 200 mg/dL (n = 94)</td>
<td>7</td>
<td>715</td>
<td>9.8</td>
<td>7.0 (2.9–6.9)</td>
<td>6.3 (2.6–15.4)</td>
</tr>
</tbody>
</table>

CI = confidence interval; RH = relative hazards.

*Adjusted for age, sex, race, and body mass index.
†Adjusted for age, sex, race, fasting glucose, and body mass index.

2HG at baseline were characterized by a large number of DM risk factors (older age, higher triglycerides, and greater obesity) that are easier to obtain than a 2HG value. Furthermore, those with baseline 2HG of 200 mg/dL or higher who subsequently developed DM were more likely to be non-Caucasian and obese and to have elevated systolic blood pressure. This finding may suggest that little is gained by the addition of a 2HG test in older individuals with FG less than 100 mg/dL beyond that provided by traditional DM risk factors. These findings, in addition to considering the poor reproducibility and rare routine use of 2HG testing in the United States, would seem consistent with the expert committee’s 1997 ADA diagnostic criteria revisions where routine use of 2HG testing was no longer emphasized [1].

Attention must be given to the additional information derived by 2HG screening (or potentially lost without 2HG screening) with regard to progression to a FG disorder. Of the 94 persons identified at baseline as having DM according to 2HG measurement, 87 (93%) were at no point subsequently identified as having DM by 2 additional FG measurements and/or annual diabetic medication inventories during 9 years of follow-up. If following the ADA recommendations where the current standard for DM diagnoses is FG, a clinical judgment ultimately must be made regarding the additional information that would be acquired from a 2HG test relative to the potential information unavailable by not performing the test. If the results of the 2HG screen are used in a manner to prevent evolution of diabetes (or draw attention to the individual having a higher risk of decompensation with serious DM-related illness), 2HG screening may be worthwhile.

An advantage of our study is that we evaluated 2HG and DM risks focusing upon men and women over age 65 years with normal FG based upon the most recent (2003) ADA criteria [3]. Although additional studies in CHS and elsewhere have evaluated FG and 2HG in the elderly, we specifically draw attention to a population with normal FG by the most recent ADA criteria while evaluating the usefulness of additional 2HG screening [4,9,11,14,18]. Our results are consistent with an analysis of 6 prospective DM studies demonstrating 2HG as a strong risk factor predicting incident DM above and beyond FG alone [19]. Another advantage of CHS is the availability of extensive longitudinal diabetes risk factor information in a community-dwelling population. It is important to recognize that in calculating incidence rates we used FG measures (potentially 2) and initiation of diabetic medications as markers for DM, and we used one 2HG measure for 7-year follow-up comparisons. These methods, limited by the availability of our data, should not be considered the gold standard for DM diagnosis [1–3].

Finally, 4% of the cohort did not have a 2HG test due to either the test being contraindicated (eg, patients who had started diabetic medications) or simply not performed (eg, patient preference), both scenarios likely to be seen in the community setting as well. It is possible that the number of new-onset DM cases is higher using 2HG and the WHO diabetes diagnostic criteria, as shown previously in CHS [4]. We evaluated only those with both glucose measures available with regard to diabetes outcomes. This is likely the largest number of elderly individuals with FG and 2HG measurements available for this type of follow-up.

In conclusion, the rate of new DM in a primarily elderly, non-Hispanic Caucasian population with normal FG is low. While a 2HG value of 200 mg/dL or higher is predictive of subsequent DM, the absolute number of cases identified is small. The additional cost and burden of obtaining such a test may or may not justify its routine use when other DM risk factors are more easily obtained. If the additional new DM cases identified do not justify the cost and burden of 2HG screening, our results suggest that FG in addition to routine DM risk factor screening may be adequate for DM risk evaluation.

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References