Fasting and 2-Hour Postchallenge Serum Glucose Measures and Risk of Incident Cardiovascular Events in the Elderly

The Cardiovascular Health Study

Nicholas L. Smith, PhD, MPH; Joshua I. Barzilay, MD; Douglas Shaffer, MD, MHS; Peter J. Savage, MD; Susan R. Heckbert, MD, PhD; Lewis H. Kuller, MD, DrPH; Richard A. Kronmal, PhD; Helaine E. Resnick, PhD, MPH; Bruce M. Psaty, MD, PhD

Background: The contributions of fasting and 2-hour postchallenge glucose level to cardiovascular events remain ill-defined, especially for nondiabetic adults. This study examined the relative predictive power of fasting and 2-hour glucose level on cardiovascular event risk.

Methods: A total of 4014 community-dwelling adults 65 years or older who participated in the baseline visit of the Cardiovascular Health Study and who were without treated diabetes or previous myocardial infarction or stroke were eligible for analyses. Participants with treated diabetes at baseline were excluded. Incident myocardial infarction or stroke, or coronary death, was the outcome of interest. Age-, sex-, and race-adjusted proportional hazards regression models described individual and joint associations between baseline measures of fasting and 2-hour postchallenge glucose level and event risk.

Results: There were 764 incident cardiovascular events during 8.5 years of follow-up. Fasting glucose level of 115 mg/dL (6.4 mmol/L) or more was associated with an increased cardiovascular risk (hazard ratio [HR], 1.66 [95% confidence interval (CI), 1.39-1.98]) in adjusted analyses compared with fasting glucose level less than 115 mg/dL. Two-hour glucose level was associated with a linear risk (HR, 1.02 [95% CI, 1.00-1.04] per 10 mg/dL [0.6 mmol/L]) that included an additional increase in risk for 2-hour glucose level of 154 mg/dL (8.5 mmol/L) or more (HR, 1.29 [95% CI, 1.04-1.59]) in adjusted analyses. In joint fasting and 2-hour glucose models, only 2-hour glucose level remained predictive of event risk.

Conclusions: Two-hour glucose level was better than fasting glucose level alone at identifying older adults at increased risk of major incident cardiovascular events.

Arch Intern Med. 2002;162:209-216

I N 1997, THE American Diabetes Association (ADA) revised diabetes diagnostic criteria by lowering the fasting plasma glucose threshold and by recommending against the routine use of glucose challenge testing, especially as it concerns epidemiologic studies.1 The change was justified primarily by epidemiologic data indicating that the new criteria would identify roughly the same number of people with microvascular complications as the previous criteria, without the burden of glucose challenge testing. These revised criteria have prompted the research community to examine the effects of the diagnostic change on the identification of persons at risk for cardiovascular disease (CVD), the primary complication of glucose disorders in old age, and all-cause mortality.2,3 Findings indicate that the current ADA criteria do not maximize the identification of persons at risk for these major health outcomes. Nonetheless, the individual and joint associations of fasting and 2-hour glucose measures with cardiovascular morbidity and mortality remain ill-defined, especially for those who do not meet 1997 ADA diabetes criteria.

In this study, we examined the relative predictive power of fasting and 2-hour postchallenge glucose level on fatal and nonfatal myocardial infarction and stroke and on cardiovascular mortality among a cohort of older adults, none of whom had treated diabetes at study entry.

RESULTS

There were 386 participants (7% of the original cohort) with pharmacologically treated diabetes at baseline and 585 (11% of the original cohort) with a baseline history of myocardial infarction or stroke who were not eligible for these analyses. From among the 4230 remaining participants, 184 participants (4%) who were missing fasting or 2-hour glucose measures and 32
SUBJECTS AND METHODS

SETTING AND DESIGN

The Cardiovascular Health Study (CHS) is a population-based, prospective cohort study of risk factors for CVD in the elderly. Participants were recruited from 4 US communities (Washington County, Maryland; Pittsburgh [Allegheny County], Pa; Forsyth County, North Carolina; and Sacramento County, California) on the basis of a randomly generated sampling frame from Health Care Financing Administration files. Annual examinations began in June 1989 and ended in June 1999.

SUBJECTS

The CHS cohort consisted of 5201 community-dwelling adults 65 years and older who participated in the baseline clinic visit in 1989 to 1990 (original cohort) and an additional 687 African American adults 65 years or older who were recruited in 1992 to 1993 (new cohort). Baseline postchallenge glucose testing was not done in the new cohort, so these participants were not included in this report. Approximately 57% of eligible participants participated in the study. Nonparticipants were more likely to be older and less educated and to have more self-reported CVD and hypertension. All study participants gave informed consent for their participation according to guidelines of the appropriate institutional review boards.

This study excluded participants with missing fasting or 2-hour glucose measures (see "Measures") and those who reported using insulin or an oral hypoglycemic agent at the baseline medication inventory. Self-reported history of diabetes was not a criterion for exclusion, although 28% of participants with self-reported diabetes and not using antidiabetic medication opted not to undergo glucose challenge testing. The study population was further restricted to participants who did not have a baseline history of myocardial infarction or stroke, to investigate the risk of incident cardiovascular events. We did not exclude participants with a history of other clinical or subclinical cardiovascular conditions, since we were interested in the primary prevention of major coronary and cerebrovascular atherosclerotic or thrombotic events, namely, myocardial infarction and stroke.

MEASURES

At the baseline examination, venipuncture was performed on study participants under 12-hour fasting conditions early during the study visit. Serum glucose was measured (Kodak Ektachem 700 Analyzer; Eastman Kodak Corp, Rochester, NY). After the fasting venipuncture, 75 g of glucose was given orally to consenting nondiabetic participants. A second venipuncture was performed 2 hours after the glucose challenge.

Covariate baseline measures included demographic characteristics (age, sex, race [white vs other], and self-reported health [good, very good, or excellent vs fair or poor]), cardiovascular risk factors (body mass index [weight in kilograms divided by the square of height in meters], current smoker, currently treated hypertension, sitting diastolic and systolic blood pressure, and low-density lipoprotein cholesterol level), clinical CVD (history of angina, coronary revascularization, congestive heart failure, or transient ischemic attacks; electrocardiogram-identified atrial fibrillation), and subclinical CVD (no clinical CVD, ankle-arm index ≤0.9, maximum internal or common carotid wall thickness >80th percentile [≥2.06 and ≥1.16 mm, respectively], carotid stenosis >25%, major electrocardiogram abnormalities [ventricular conduction defect, major Q-wave abnormalities, left ventricular hypertrophy, isolated ST–T-wave abnormalities, atrial fibrillation, and
threshold model where the risk of an incident CVD event increased at the 85th percentile of fasting glucose level (≥115 mg/dL [≥6.4 mmol/L]) was the best fitting model. This stepped increase was associated with a 66% increase in CVD event risk (HR, 1.66; 95% CI, 1.39-1.98) compared with those with baseline fasting glucose level less than 115 mg/dL. For CAD and CBD outcomes, this corresponded to a 62% and 84% increase in risk, respectively. No interactions were detected between a fasting glucose threshold and either sex or CVD for all cardiovascular events.

For 2-hour glucose level, age-, sex-, and race-adjusted analyses demonstrated that a combined linear and threshold model fit the data best. In this model, there was a 2% increase in risk of an incident CVD event for every 10-mg/dL (0.6-mmol/L) increase in 2-hour glucose level (HR, 1.02; 95% CI, 1.00-1.04) plus an additional 29% increase in risk for all values above the 65th percentile (≥154 mg/dL [≥8.5 mmol/L]) (HR, 1.29; 95% CI, 1.04-1.59). This held true for CAD and CBD outcomes where there was a 2% linear increase in addition to a 28% (CAD) and 42% (CBD) increase in event risk for 2-hour glucose values of 154 mg/dL (8.5 mmol/L) or more. No interactions were detected between linear and threshold 2-hour glucose levels and either sex or CVD for all events.

JOINT CONTRIBUTIONS OF FASTING AND 2-HOUR GLUCOSE LEVELS

Table 2 presents relative risks for quintiles of fasting (top rows) and 2-hour (bottom rows) glucose levels in 3 models. For fasting glucose, adding a continuous measure of 2-hour glucose to the age-, sex-, and race-adjusted model produced a better fitting model (P <.001) and largely removed the association between fasting glucose level and incident CVD event risk. Additional adjustments for smoking, blood pressure, hypertension treatment, low-density lipoprotein cholesterol level, body mass index, self-reported health, and clinical and subclinical CVD had trivial effects on the fasting glucose level–CVD association. Concerning 2-hour glucose level, adding a continuous measure of fasting glucose to the age-, sex-, and race-adjusted model did not produce a better fitting model (P = .40) and did not change the association between 2-hour glucose level and CVD event risk. Adjusting further for known CVD risk factors slightly diminished the predictive power of 2-hour
When analyses excluded participants with diabetic-level fasting glucose values, risk estimates changed by no more than 5% in any stratum.

**ANALYSES STRATIFIED BY FASTING GLUCOSE LEVEL**

**Table 3** presents the number of incident CVD events, unadjusted event rates, and age-, race-, and sex- (where appropriate) adjusted hazard ratios for each 2-hour glucose category according to fasting glucose strata. Among participants with normal fasting glucose levels, the CVD event rate increased with each stratum of 2-hour glucose. This observation generally held true for event type, sex, and prevalent CVD strata, although events were limited in the top 2-hour glucose stratum for those without CVD. Exploratory analyses showed that a threshold increase in CVD event risk of 83% for 2-hour glucose values of 161 mg/dL (8.9 mmol/L) or more fit the data best (HR, 1.83; 95% CI, 1.29-2.60). This model did not vary by event type or by sex or prevalent CVD strata, although person-years and events were sparse in some strata. The diabetic stratum of fasting glucose level is not presented in Table 3 since, among this stratum, 73% of the person-years and 72% of the events were in the 2-hour glucose stratum of 200 mg/dL (11.1 mmol/L) or more. This resulted in too few person-years (n=518) and events (n=21) in the remaining 2-hour glucose strata to calculate meaningful rates and age-, sex-, and race-adjusted relative rates.

Among the 3137 participants with normal fasting glucose levels, there were 548 incident CVD events (17%), of which 5% were attributable to 2-hour glucose levels of 140 mg/dL (7.8 mmol/L) or more and 1% were attributable to 2-hour glucose levels of 200 mg/dL (11.1 mmol/L) or more in adjusted models according to population attributable risk estimates. Among the 592 participants with impaired fasting glucose, there were 141 incident CVD events (24%), of which 24% were attributable to 2-hour glucose levels of 140 mg/dL (7.8 mmol/L) or more in adjusted models according to population attributable risk estimates.
more and 12% were attributable to levels of 200 mg/dL (11.1 mmol/L) or more in adjusted models.

Participants with isolated postchallenge hyperglycemia accounted for 329 (8%) of the 4014 participants at baseline. In age-, sex-, and race-adjusted multivariate modeling, isolated postchallenge hyperglycemia was associated with a 53% increase in CVD event risk relative to participants with 2-hour glucose values of 139 mg/dL (7.7 mmol/L) or less (HR, 1.53; 95% CI, 1.22-1.92). Similar results were found for CHD (HR, 1.55; 95% CI, 1.16-2.05) and CBD (HR, 1.65; 95% CI, 1.20-2.27), for women (HR, 1.67; 95% CI, 1.26-2.26) and men (HR, 1.34; 95% CI, 0.94-1.91), and for participants with CVD (HR, 1.59; 95% CI, 1.25-2.02). Isolated postchallenge hyperglycemia was not associated with increased event risk for participants without CVD (HR, 0.78; 95% CI, 0.40-1.54).

**COMMENT**

In this study of older adults without treated diabetes at study entry, both fasting and 2-hour glucose levels were individually associated with an increased risk of incident CVD events, but only 2-hour glucose values were predictive of CVD events in models that included both glycemria measures. Among participants with normal and impaired fasting glucose levels, impaired glucose tolerance and diabetic-level 2-hour glucose values were associated with an increased risk of CVD events. These relationships were similar for CHD and CBD outcomes, did not vary by sex, and were similar for participants with prevalent clinical or subclinical CVD at study entry. Among study participants without prevalent CVD, evidence of a glycemria-CVD association was limited.

These prospective data provide evidence that an elevated 2-hour glucose level is a useful risk factor for identifying older adults who are at increased risk of a CVD event, which occurred in 20% of the study participants after 8.5 years of follow-up. Besides predicting CVD events independent of fasting glucose level, 2-hour glucose measurement contributed additional risk information beyond fasting glucose information for participants with normal and impaired fasting glucose levels. Among participants with normal fasting glucose levels, above-normal 2-hour glucose values accounted for 1 of 20 incident CVD events, and among those with impaired fasting
The primary strengths of this study include population-based sampling, standardized glucose measurements to assess glycemia, extensive CVD risk factor measurements, and complete follow-up for morbid and fatal events. Several limitations merit discussion, however. First, only 1 measure each of fasting and 2-hour glucose was available at baseline. This method is standard for most epidemiologic studies in which populations and not individuals are studied. According to ADA clinical practice guidelines, a diagnosis of diabetes requires a confirmatory test...
Since an elevated glucose measure was not confirmed by a second measure, we cannot be certain that any glucose classification was correct and not the result of random fluctuations in glycemia. Second, nearly 43% of people originally contacted to participate in the CHS refused participation. Those who participated tended to be healthier than those who refused participation, and this fact may limit the generalizability of the findings. Third, in some analytic strata, there were too few events and person-years to produce sufficiently narrow confidence limits to draw meaningful conclusions. Fourth, the cohort averaged 73 years of age at entry, so data and results cannot be generalized to younger populations. Last, although this study is primarily observational, information from the annual clinic visits was shared with participants’ physicians and may have influenced the care received by the participants after the baseline examination.25

CONCLUSIONS

Numerous cardiovascular risk factors have been identified during the past 50 years of modern epidemiologic research, and the role of glycemia is just now being defined. Any clinical or policy implications that may arise from this study must be balanced with issues of patient burden and cost as they relate to modifiable risk factors that affect health outcomes in older adults. Our findings indicate that both fasting and 2-hour postchallenge glucose levels were associated with an increased risk of major incident coronary and cerebrovascular events in older adults. Furthermore, 2-hour glucose level was better able to identify those at risk than

Table 3. Cardiovascular Event Rates per 1000 Person-Years and Age- and Sex-Adjusted Relative Hazard Estimates According to Baseline Fasting and 2-Hour Serum Glucose Levels, Cardiovascular Health Study, 1989 to 1998*

<table>
<thead>
<tr>
<th>Fasting Serum Glucose</th>
<th>Normal (≤109 mg/dL)</th>
<th>Impaired (110-125 mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-h Glucose, mg/dL</td>
<td>Events Person-Years†</td>
<td>Rates‡</td>
</tr>
<tr>
<td>All events ≤139</td>
<td>315</td>
<td>14 912</td>
</tr>
<tr>
<td>140-199</td>
<td>193</td>
<td>6931</td>
</tr>
<tr>
<td>≥200</td>
<td>40</td>
<td>1294</td>
</tr>
<tr>
<td>Total</td>
<td>548</td>
<td>23 138</td>
</tr>
<tr>
<td>CHD events ≤139</td>
<td>198</td>
<td>15 180</td>
</tr>
<tr>
<td>140-199</td>
<td>125</td>
<td>7122</td>
</tr>
<tr>
<td>≥200</td>
<td>27</td>
<td>1341</td>
</tr>
<tr>
<td>Total</td>
<td>350</td>
<td>23 643</td>
</tr>
<tr>
<td>Stroke events ≤139</td>
<td>137</td>
<td>15 332</td>
</tr>
<tr>
<td>140-199</td>
<td>85</td>
<td>7123</td>
</tr>
<tr>
<td>≥200</td>
<td>19</td>
<td>1356</td>
</tr>
<tr>
<td>Total</td>
<td>241</td>
<td>23 811</td>
</tr>
<tr>
<td>Men ≤139</td>
<td>155</td>
<td>5482</td>
</tr>
<tr>
<td>140-199</td>
<td>97</td>
<td>2470</td>
</tr>
<tr>
<td>≥200</td>
<td>13</td>
<td>402</td>
</tr>
<tr>
<td>Total</td>
<td>265</td>
<td>8354</td>
</tr>
<tr>
<td>Women ≤139</td>
<td>160</td>
<td>9432</td>
</tr>
<tr>
<td>140-199</td>
<td>96</td>
<td>4462</td>
</tr>
<tr>
<td>≥200</td>
<td>27</td>
<td>892</td>
</tr>
<tr>
<td>Total</td>
<td>283</td>
<td>14 785</td>
</tr>
<tr>
<td>No CVD ≤139</td>
<td>94</td>
<td>7378</td>
</tr>
<tr>
<td>140-199</td>
<td>48</td>
<td>3021</td>
</tr>
<tr>
<td>≥200</td>
<td>6</td>
<td>428</td>
</tr>
<tr>
<td>Total</td>
<td>148</td>
<td>10 827</td>
</tr>
<tr>
<td>CVD ≤139</td>
<td>221</td>
<td>7536</td>
</tr>
<tr>
<td>140-199</td>
<td>145</td>
<td>3910</td>
</tr>
<tr>
<td>≥200</td>
<td>34</td>
<td>866</td>
</tr>
<tr>
<td>Total</td>
<td>400</td>
<td>12 312</td>
</tr>
</tbody>
</table>

*To convert glucose level to millimoles per liter, multiply by 0.0555. CHD indicates coronary heart disease; CVD, cardiovascular disease.
†Because of rounding, totals may not sum exactly.
‡Event rate per 1000 person-years.
§Age-, race-, and sex- (where appropriate) adjusted hazard ratios (HR) and 95% confidence intervals (CI) calculated by means of proportional hazards regression.

The information of elevated glucose measures on a subsequent day. Since an elevated glucose measure was not confirmed by a second measure, we cannot be certain that any glucose classification was correct and not the result of random fluctuations in glycemia. Second, nearly 43% of people originally contacted to participate in the CHS refused participation. Those who participated tended to be healthier than those who refused participation, and this fact may limit the generalizability of the findings. Third, in some analytic strata, there were too few events and person-years to produce sufficiently narrow confidence limits to draw meaningful conclusions. Fourth, the cohort averaged 73 years of age at entry, so data and results cannot be generalized to younger populations. Last, although this study is primarily observational, information from the annual clinic visits was shared with participants’ physicians and may have influenced the care received by the participants after the baseline examination.25

Numerous cardiovascular risk factors have been identified during the past 50 years of modern epidemiologic research, and the role of glycemia is just now being defined. Any clinical or policy implications that may arise from this study must be balanced with issues of patient burden and cost as they relate to modifiable risk factors that affect health outcomes in older adults. Our findings indicate that both fasting and 2-hour postchallenge glucose levels were associated with an increased risk of major incident coronary and cerebrovascular events in older adults. Furthermore, 2-hour glucose level was better able to identify those at risk than...
fasting glucose level alone. Although a 2-hour measure of glycemia is burdensome in routine clinical practice, it may serve a role in identifying older adults at increased risk of incident cardiovascular events.

Accepted for publication May 8, 2001.

This study was supported by contracts N01-HC-85079, N01-HC-85080, N01-HC-85081, N01-HC-85082, N01-HC-85083, N01-HC-85084, N01-HC-85085, N01-HC-85086, N01-HL-35129, and N01-HL-15103 from the National Heart, Lung, and Blood Institute and grant R01-AG-03536 from the National Institute on Aging, Bethesda, Md.

We thank Melissa L. Anderson, MS, for her thoroughness and diligence in verifying the statistical results in this article.

Corresponding author and reprints: Nicholas L. Smith, PhD, MPH, Cardiovascular Health Research Unit, 1730 Minor Ave, Suite 1360, Seattle, WA 98101 (e-mail: nlsmith@u.washington.edu).

REFERENCES


