Postchallenge Hyperglycemia and Mortality in a National Sample of U.S. Adults

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OBJECTIVE — Although postchallenge hyperglycemia is a well-established feature of type 2 diabetes, its association with risk of mortality is uncertain. Therefore, the aim of this study was to assess the independent association of fasting and 2-h glucose levels with all-cause and cardiovascular disease (CVD) mortality.

RESEARCH DESIGN AND METHODS — We analyzed data from the Second National Health and Nutrition Examination Survey (NHANES II) Mortality Study, a prospective cohort study of U.S. adults examined in the NHANES II, and focused on the 3,092 adults aged 30–74 years who underwent an oral glucose tolerance test at baseline (1976–1980). Deaths were identified from U.S. national mortality files from 1976 to 1992. To account for the complex survey design, we used SUDAAN statistical software for weighted analysis.

RESULTS — Compared with their normoglycemic counterparts (fasting glucose [FG] <7.0 and 2-h glucose <7.8 mmol/l), adults with fasting and postchallenge hyperglycemia (FG ≥7.0 and 2-h glucose ≥11.1 mmol/l) had a twofold higher risk of death after 16 years of follow-up (age- and sex-adjusted relative hazard [RH] 2.1, 95% CI 1.4–3.2). However, adults with isolated postchallenge hyperglycemia (FG <7.0 and 2-h glucose ≥11.1 mmol/l) were also at higher risk of death (1.6, 1.0–2.6). In proportional hazards analysis, FG (fully adjusted RH 1.10 per 1 SD; 95% CI 1.01, 1.22) and 2-h glucose (1.14, 1.00–1.29) showed nearly identical predictive value for mortality. Similar trends were observed for CVD mortality.

CONCLUSIONS — These results suggest that postchallenge hyperglycemia is associated with increased risk of all-cause and CVD mortality independently of other CVD risk factors.

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Postchallenge hyperglycemia (PCH), typically defined as 2-h glucose levels >11.1mmol/l, is an established feature of diabetes and has been associated with worsening cardiovascular disease (CVD) risk profile (1). It is estimated that 6.2% of adults aged 40–74 years in the U.S. have PCH (2). The prevalence of PCH with normal fasting glucose has been estimated to be 48% in men and 70% in women >65 years of age with previously undiagnosed diabetes (3). The association of an increased risk of all-cause and CVD mortality with hyperglycemia has been reported in a number of populations (4,5–19,20). However, few of these previous studies have been conducted in a sample representative of the general U.S. population (4,5–19,20). Moreover, it is unclear whether this excess mortality is conferred by PCH per se or rather by fasting hyperglycemia or CVD risk factors that commonly accompany diabetes, such as high blood pressure, dyslipidemia, and obesity (1,21–25). Although there is mounting evidence of the importance of PCH, the prognostic value of this measure in the general U.S. population, especially as it relates to mortality, remains unclear.

Therefore, we sought to evaluate the association of 2-h postchallenge blood glucose levels with mortality in a U.S. nationally representative sample. If independently predictive, PCH might represent a specific target for interventions to reduce diabetes-related mortality.

RESEARCH DESIGN AND METHODS

Data sources

Data were obtained from the Second National Health and Nutrition Survey (NHANES II) mortality study, a prospective cohort study which passively followed participants >30 years of age who underwent a detailed examination in NHANES II (n = 9,250). NHANES II was conducted between 1976 and 1980 by the National Center for Health Statistics. A stratified multistage sample design was used to produce a representative sample of the noninstitutionalized U.S. civilian population between the ages of 6 months and 74 years (26). The survey included a household interview, a physical examination, laboratory tests, and detailed questionnaires on health- and nutrition-related topics. The response rate for adults 20–74 years of age selected for the examination was 68% (27).

Participants

Among adults aged 30–74 years, 4,664 were selected at random for the oral glucose tolerance test (OGTT) and asked to fast overnight if they did not report having diabetes and were not currently using

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Abbreviations: ADA, American Diabetes Association; CVD, cardiovascular disease; FG, fasting glucose; IGT, impaired glucose tolerance; NHANES II, Second National Health and Nutrition Examination Survey; OGTT, oral glucose tolerance test; PCH, postchallenge hyperglycemia; RH, relative hazard; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

insulin. Individuals were excluded from the analysis if they had a fasting time <9 h or >17 h, a 2-h OGTT duration <105 min or >135 min, or a missing fasting glucose or 2-h glucose value (n = 1,508). In addition, we excluded 64 participants from the analytic cohort who were missing data on HDL cholesterol, smoking, physical activity, or blood pressure. Thus, we analyzed data on 3,092 adults without insulin-requiring diabetes who had valid data on glucose tolerance and other CVD risk factors.

Baseline assessments

Each participants age at interview, sex, race (white, nonwhite), years of education (less than high school or greater than high school), and personal health characteristics were obtained by interview. Smoking status was categorized as "ever" or "never." Participants were asked to rate both their recreational and nonrecreational physical activity as "much," "moderate," or "little to no activity." Responses for both questions were added and recoded, ielding the following categories: moderate to low activity (low activity in both or low activity in one and moderate activity in the other) and moderate to high activity (moderate activity in both or moderate activity in one and high activity in the other). Participants were defined as having CVD at baseline if they tested positive on a modified Rose Angina Questionnaire or answered "yes" to any of the following questions from the medical history questionnaire: "Has a doctor ever told you that you had a heart attack?" or "Have you ever had a stroke?" and "Did a doctor tell you this?" (26). Participants were defined as having previously diagnosed diabetes if they answered "yes" to both of the following questions: "Do you have glucose diabetes?" and "Did a doctor tell you that you had it?" (n = 96). Of the 96 participants who had diagnosed diabetes, 43 participants reported current use of oral diabetic medications.

Physical examination included standardized measurements of height, weight, and blood pressure (26). BMI was calculated as weight in kilograms divided by the square of the height in meters. BMI of the participants was categorized as <25, 25–26.9, 27–29.9, and ≥30 kg/m^2 (28). We used the average of two blood pressure readings for each participant in the sitting position. Laboratory measures, including standard blood assays for total serum cholesterol, HDL, and plasma glucose levels, were analyzed from blood samples of participants who fasted overnight for 10–16 h (26). For each participant, a total cholesterol–to–HDL cholesterol ratio was calculated. After a fasting blood sample was taken, participants ingested 75 g glucose (26). A subsequent blood sample was taken at 120 ± 15 min after the OGTT in each participant. Participants were characterized by glucose tolerance using both the 1997 American Diabetes Association (ADA) (29) and the 1998 World Health Organization (WHO) classification (30).

Outcomes

Mortality status was ascertained for the years 1976–1992 by searching the National Death Index and the Social Security Administration Death master file (31). There was no censoring or loss to follow-up in this cohort; participants not found to be deceased by 31 December 1992 were assumed to be alive at that time. Deaths were ascribed to CVD if the underlying cause of death according to the International Classification of Diseases, 9th revision, was coded from 401.0–448.9.

Analysis

Weighting to the U.S. population. Baseline and proportional hazard estimates were weighted to the U.S. population at the midpoint of NHANES II (1 March 1978). SUDAAN statistical software (version 6.4; Research Triangle Park, NC) was used to account for the complex survey design and to thereby provide nationally representative estimates (26,32).

Baseline characteristics. Demographic characteristics and cardiovascular risk factors at baseline were described for the participants. Baseline comparisons by 2-h glucose group (2-h glucose <11.1 or ≥11.1 mmol/l) for demographic risk factors (age, sex, race, and education), behavioral risk factors (physical activity and smoking), biological risk factors (total cholesterol, fasting glucose levels, total cholesterol–to–HDL ratio, systolic blood pressure, diastolic blood pressure, and BMI), and reported history of CVD were completed using analysis of covariance or Pearson χ^2 test. All tests of significance were two-tailed (P = 0.05), with no corrections for multiple comparisons.

Proportional hazards analysis. To study the independent association of 2-h blood glucose with mortality, several multivariate proportional hazards models were performed to evaluate *1*) PCH and impaired glucose tolerance (IGT) by fasting glucose levels, *2*) fasting and 2-h glucose as continuous variables, and *3*) the glucose tolerance groups under WHO and ADA criteria. The above-mentioned demographic (age, sex, race, and education), behavioral (physical activity and smoking) and biological factors (BMI, systolic blood pressure, and total cholesterol–to–HDL cholesterol ratio) were used as covariates.

These models were first performed separately using fasting and 2-h glucose as main independent continuous variables and then simultaneously using both variables. SDs for fasting glucose and 2-h glucose were estimated in each of the subgroup analysis and were used to estimate the relative risk of death to the change in 1 SD of fasting or 2-h blood glucose.

Subgroup analyses were first performed excluding only participants with diagnosed diabetes, again excluding only participants with CVD at baseline, and finally excluding participants with either diagnosed diabetes or CVD at baseline.

First-order interactions between glucose and all of the included covariates were tested. Graphs of log-log plot of the relative hazards by time were used to check the assumption of proportionality.

RESULTS

Characteristics and risk factors at baseline

Table 1 summarizes the characteristics of the cohort by 2-h postchallenge glucose level at baseline. Compared with their counterparts with 2-h glucose <11.1 mmol/l, those with PCH were older and less educated. They were also more frequently obese, had known diabetes, had a previous history of CVD, and had higher levels of total cholesterol–to–HDL cholesterol ratio, blood pressure, and fasting glucose.

Mortality

There were 661 deaths (21%) during 41,610 person-years of follow-up. The crude all-cause death rate per 1,000 person-years was highest (39.0%) for participants with PCH and fasting glucose ≥7.0 mmol/l, followed by participants with fasting glucose <7.0 mmol/l and IGT

Table 1—*Baseline characteristics of 3,092 NHANES II participants aged 30 to 74 years by 2-h postchallenge glucose level*

	2-h glucose <11.1 mmol/l (n = 2,856)	2-h glucose ≥11.1 mmol/l (n = 236)
Age (years)*	48.8 ± 0.30	58.2 ± 1.03
Female (%)	53.9	58.7
White (%)	89.5	84.5
Education less than high school (%)*	34.5	52.9
Ever smoker (%)	61.7	57.6
Physical activity (i.e., low to moderate)	25.2	32.8
Systolic blood pressure (mmHg)*	127.3 ± 0.83	143.7 ± 1.96
Diastolic blood pressure (mmHg)*	79.1 ± 0.53	84.3 ± 0.81
BMI kg/m^2 (%)*		
<25	49.9	24.4
25 ≤ to <27	17.6	14.6
27 ≤ to <30	17.6	19.6
≥30	14.9	41.4
Total cholesterol–to–HDL cholesterol ratio	4.7 ± 0.06	5.4 ± 0.18
Fasting plasma glucose (mmol/l)*	5.1 ± 0.02	7.7 ± 0.23
History of CVD (%)*	8.6	20.4
Diagnosed diabetes (%)*	1.5	19.7

Data are means ± SD or %. *$P < 0.05$ for comparison of those with 2-h glucose <11.1 mmol/l vs. 2-h glucose ≥11.1 mmol/l.

(21.0% for 2-h 7.8–11.1 mmol/l) or PCH (29.3% for 2-h ≥11.1 mmol/l), and lowest (13.1%) for participants with normal glucose levels (Table 2). A similar CVD mortality pattern was observed. After adjusting for age and sex, this corresponds to a 110% increased risk of mortality for participants with PCH and fasting glucose ≥7.0 mmol/l, a 30% increased risk for participants with 2-h glucose ≥7.8 and <11.1 mmol/l and fasting glucose <7.0 mmol/l, and a 60% increased risk for participants with PCH and fasting glucose <7.0 mmol/l.

Multivariate proportional hazards

After simultaneous adjustment for age, sex, race, education, smoking, physical activity, BMI, systolic blood pressure, and total cholesterol–to–HDL cholesterol ratio, individuals with PCH had a slight increased risk of death for both all-cause and CVD mortality (Table 2). However, the relative hazard estimate was only statistically significant for participants with fasting glucose ≥7.0 mmol/l and 2-h glucose ≥11.1 mmol/l (Table 2). When participants with diagnosed diabetes were excluded, the risk of all-cause mortality was slightly attenuated for each group but still highest for those with fasting glucose ≥7.0 mmol/l and 2-h glucose ≥11.1 mmol/l (relative hazard [RH] 1.5, 95% CI 0.8–3.0), followed by 2-h glucose ≥11.1 mmol/l and fasting glucose <7.0 mmol/l (1.2, 0.6–2.4), and lowest for fasting glucose <7.0 mmol/l and 2-h glucose ≥7.8 and <11.1 mmol/l (1.1, 0.8–1.6).

A 10% increased risk of mortality from all-cause mortality was associated with a 1-SD increase in fasting glucose (1.18 mmol/l) and a 14% increased risk with a 1-SD increase in 2-h glucose (3.18 mmol/l) after adjusting for age, sex, race, smoking status, physical activity, BMI, systolic blood pressure, and total cholesterol–to–HDL cholesterol ratio (Table 3), but the lower limit of the 95% CI was the null value. Similar estimates were obtained for CVD mortality, but the 95% CI included the null value. When fasting and 2-h glucose were included in the same multivariate proportional hazards model, the RHs estimated were similar in magni-

Table 2—*All-cause and cardiovascular disease mortality by fasting and 2-h postchallenge glucose group for 3,092 adults aged 30 to 74 years in NHANES II*

	Fasting plasma glucose <7.0 mmol/l			Fasting plasma glucose ≥7.0 mmol/l		
	2-h plasma glucose (mmol/l)			2-h plasma glucose (mmol/l)		
	<7.8	7.8 to 11.1	≥11.1	<7.8	7.8 to 11.1	≥11.1
Participants	2,321	503	131	9	23	105
Person years	31,877	6,533	1,604	125	241	1,230
Deaths	416	137	47	2	11	48
CVD deaths	181	59	23	0	8	27
All-cause						
Mortality per 1,000 PY	13.1	21.0	29.3	16.0	45.6	39.0
RH (95% CI)*	1.0 Reference	1.3 (1.0, 1.6)	1.6 (1.0, 2.6)	—	—	2.1 (1.4, 3.2)
RH (95% CI)†	1.0 Reference	1.1 (0.8, 1.6)	1.3 (0.7, 2.5)	—	—	1.9 (1.1, 3.2)
CVD death						
Mortality per 1,000 PY	5.7	9.0	14.3	0	33.2	22.0
RH (95% CI)*	1.0 Reference	1.1 (0.7, 1.5)	1.4 (0.8, 2.5)	—	—	2.3 (1.4, 3.6)
RH (95% CI)†	1.0 Reference	1.0 (0.6, 1.6)	1.3 (0.6, 2.8)	—	—	1.6 (0.8, 3.4)

Data are n unless otherwise stated. — Too few events for stable estimate. *RH and 95% CI adjusted for age (continuous) and sex; †adjusted for age (continuous), sex, race (white, nonwhite), education (<high school, ≥high school), smoking (ever, never), physical activity (low, high), BMI (<25, 25≤ to <27, 27≤ to <30, ≥30 kg/m^2), systolic blood pressure, and total cholesterol–to–HDL cholesterol ratio (continuous). PY, person years.

Table 3—*RH and 95% CI for all-cause and CVD mortality for 1 SD increment in plasma glucose for 3,092 adults aged 30–74 years in NHANES II*

	All-cause mortality		CVD Mortality	
	Fasting glucose	2-h glucose	Fasting glucose	2-h glucose
Model 1				
RH	1.10	1.14	1.09	1.13
95% CI	1.00–1.22	1.00–1.29	0.95–1.25	0.93–1.38
P value β	0.02	0.03	0.56	0.61
Model 2				
RH	1.05	1.10	1.02	1.07
95% CI	0.89–1.23	0.91–1.33	0.79–1.32	0.78–1.46
P value β	0.37	0.59	0.85	0.67

Model 1, proportional hazards model adjusts for either fasting or 2-h glucose; model 2, proportional hazards model adjusts for fasting and 2-h glucose simultaneously. SD for fasting glucose 1.18 mmol/l and for 2-h glucose 3.18 mmol/l. *Adjusted for age (continuous), sex, race (white, nonwhite), education (<high school, ≥high school), smoking (ever, never), physical activity (low, high), BMI (<25, 25≤ to <27, 27≤ to <30, ≥30 kg/m^2), systolic blood pressure, total cholesterol–to–HDL cholesterol ratio (continuous).

tude as when each were modeled separately (Table 3). However, the 95% CI included the null value, and the *P*-value for the β-coefficient was >0.05 (Table 3). Analysis was repeated, excluding participants with diagnosed diabetes, CVD at baseline, or either diagnosed diabetes or CVD at baseline, and similar results for both all-cause and CVD mortality were obtained (data not shown).

Finally, we compared 1997 ADA and 1998 WHO criteria in predicting mortality because WHO criteria apply 2-h postchallenge glucose values, whereas ADA criteria do not. In general, WHO criteria categories yielded risk estimates that were slightly stronger than those of ADA criteria. For example, with regard to all-cause mortality and after adjusting for all of the above-mentioned covariates, compared with participants with normal glucose tolerance, participants with diagnosed diabetes at baseline had the greatest HR ratio by both WHO and ADA criteria (Table 4). Participants with undiagnosed or diagnosed diabetes had an increased, but nonsignificant, risk of mortality by both WHO and ADA criteria (Table 4). Based on the WHO definition, participants with IGT had a 14% increased risk of mortality, and based on the ADA definition, participants with impaired fasting glucose had an 8% increased risk of mortality compared with those with normal glucose (Table 4). Similar, albeit nonsignificant, patterns were observed for CVD mortality (Table 4).

CONCLUSIONS — The results from this study suggest that postchallenge hyperglycemia might be independently associated with mortality in the general U.S. population. The effect is strongest in the presence of elevated fasting glucose but present when fasting plasma glucose is normal. This effect is only partially mediated by established CVD risk factors, such as concurrent abnormal blood pressure and lipids. Adjusting for fasting, the magnitude of the estimated RH of mortality associated with the continuous increase of 2-h glucose did not change; however, the 95% CI included the null value. A high correlation between fasting and 2-h glucose levels (r^2 = 0.90) was observed in our study population. Strengths of this study include its national representation and a length of follow-up ranging from 12 to 16 years.

Nevertheless, several limitations should be kept in mind. First, there was nonresponse in NHANES II at each stage of the survey and a potential misclassification of vital status. In particular, for adults age 20–74 years, only 68.0% of participants selected for the survey in the OGTT subsample completed the examination (26). However, respondents and nonrespondents did not differ significantly in demographic or health-related characteristics (27,33). Second, a person not found to be deceased as of 31 December 1992 was assumed to be alive at the end of follow-up (31). However, because vital status was determined independent of glucose tolerance status, if misclassification had occurred, it was likely to be nondifferential, therefore producing a conservative bias (34,35). Third, similar to other previous studies, the results of this study are based on baseline glucose tolerance. It is likely that participants with high fasting and 2-h plasma glucose levels progressed to diabetes during follow-up, which is known to increase the risk of both all-cause and CVD mortality.

Since 1980, there have been a number of studies investigating the relationship of postchallenge hyperglycemia and mortality (3–9,11–20). In general, these studies have found an increased risk of death with increasing postchallenge glu-

Table 4—*RH (95% CI) for all-cause and CVD mortality by 1997 ADA and 1998 WHO criteria for 3,092 adults aged 30–74 years in NHANES II*

	Normal glucose tolerance	Impaired fasting glucose	Undiagnosed diabetes	Diagnosed diabetes
ADA				
n	2,706	193	97	96
All-cause				
RH (95% CI)	Reference	1.08 (0.70–1.67)	1.41 (0.77–2.58)	1.86 (1.03–3.15)
CVD				
RH (95% CI)	Reference	0.65 (0.31–1.34)	1.23 (0.49–3.07)	1.70 (1.02–2.84)
WHO				
n	2,226	555	215	96
All-cause				
RH (95% CI)	Reference	1.14 (0.80–1.63)	1.36 (0.84–2.21)	1.89 (1.07–3.36)
CVD				
RH (95% CI)	Reference	0.93 (0.57–1.51)	1.21 (0.62–2.39)	1.76 (1.03–3.01)

Participants with impaired fasting glucose (defined as 2-h glucose <7.8 mmol/l and fasting glucose ≥6.1 and <7.0 mmol/l) (n = 76) were excluded from the analysis because of small numbers. There were 26 deaths among these participants. *Adjusted for age (continuous), sex, race (white, non-white), education (<high school, ≥high school), smoking (ever, never), physical activity (low, high), BMI (<25, 25≤ to <27, 27≤ to <30, ≥30 kg/m^2), systolic blood pressure, total cholesterol–to–HDL cholesterol ratio (continuous).

cose levels compared with normal levels. In the Chicago Peoples Gas Company study, 1-h 50-g postload glucose was measured twice (1.4 years apart) at baseline among participants without known diabetes. After 19 years of follow-up, the relative risk of death from all-causes for individuals with postchallenge glycemia ≥11.1 mmol/l, as compared with those with normal glucose levels at baseline, was 1.78 (95% CI 1.09–2.92); for CVD mortality, it was 2.42 (1.22–4.80) (20). Because postprandial glucose is known to have a high intra-individual variability, misclassification could arise when only one individual measurement is used that would bias the association toward the null. Studies with similar follow-up time of 12–25 years have also reported increased risk of death from all-causes and CVD mortality for individuals with postchallenge hyperglycemia compared with those with normal glucose levels (5,12–14). Other studies that have found similar results have been limited by relatively short follow-up (<10 years) and were not representative of the general U.S. population (3,4,6–11,15–18). In other studies, IGT was found to be a significant predictor of mortality, but IFG was not (16).

The results of this study support previous study findings from the Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study (4) that WHO criteria categories yield risk estimates that are slightly stronger than those of ADA criteria. This further suggests that OGTTs enable the identification of postchallenge hyperglycemic individuals who may have the greatest risk of death. The identification of individuals with PCH is important. First, such individuals might be offered aggressive interventions aimed at improvement of hyperglycemia and modification of other risk factors, such as hypertension, obesity, and hyperlipidemia. Second, these individuals could be identified for nonpharmacological treatments, such as weight reduction and increasing physical activity. Third, one might devise pharmacological interventions aimed specifically at the modification of PCH. In conclusion, these results suggest that PCH has predictive value for all-cause mortality and may also predict CVD mortality independently of other CVD risk factors. In addition, however, because of co-linearity, a larger study would be required to demonstrate independence from fasting glucose on epidemiological grounds alone.

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