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Association of glucose measures with total and coronary heart disease mortality: does the effect change with time? (The Rancho Bernardo Study)

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Abstract

Aims—To compare the associations of three glucose measures with coronary heart disease (CHD) and total mortality and to examine how these associations changed over time.

Methods—Prospective study of 1,774 adults (median age 68 years, 56% female). Fasting plasma glucose (FPG), 2-hour post-challenge glucose (2hPG), and glycohemoglobin (GHb) were obtained in 1984–1987. Mortality data was obtained for all participants. Multivariable Cox models examined the association of baseline glucose measures with mortality during sequential periods of follow-up (0–6, 7–12, and 13–18 years), adjusting for age, sex, blood pressure, LDL-cholesterol, smoking, exercise, and aspirin use.

Results—854 (48%) participants died during follow-up. In adjusted models, only GHb was associated with total mortality over the entire 18 years ($p=0.007$). In analyses of mortality in successive 6 year time intervals, the association of GHb and total mortality was only significant in years 0–6. For each 1% increase in GHb, the hazard ratio for death in years 0–6 was 1.14 (95% CI 1.01–1.30, $p=0.04$) and the hazard ratio for CHD death was 1.26 (95% CI 1.03–1.55, $p=0.02$). Stratification by sex and exclusion of participants with diabetes did not change our results.

Conclusions—Higher levels of GHb were associated with increased total and CHD mortality within the first six years independent of cardiac risk factors. Though further research is needed, this supports the hypothesis that early glycemic control may affect mortality outcomes.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Keywords

Diabetes mellitus; coronary disease; risk assessment; glucose; glucose tolerance test

INTRODUCTION

Hyperglycemia is a controversial predictor of total and coronary heart disease (CHD) mortality independent of other cardiac risk factors in persons with and without diabetes [1–5]. Glycemic measures, including fasting plasma glucose (FPG), 2-hour post-challenge glucose (2hPG), and glycated hemoglobin (total glycohemoglobin (GHb) and hemoglobin A1c (HbA1c)), show conflicting associations with mortality [6–12]. However, few studies had sufficient data on all three measures of glycemia to allow comparisons [7,8,13]. In addition, while the association of blood pressure, lipids, and obesity with mortality decreases with time since measurement [14], no studies have determined whether the association between glycemia and mortality varies over time.

We examined the association of three glucose measures (FPG, 2hPG, and GHb) with mortality in 1,774 community-dwelling men and women from the Rancho Bernardo Study who were followed for a maximum of 18 years. We determined the associations of baseline glucose measures with total and CHD mortality over three successive six-year intervals. In addition, we explored the effect of potential mediating variables and examined secular changes in lifestyle behaviors and medication use that could affect the association between glucose and mortality.

SUBJECTS

The Rancho Bernardo Study is a prospective cohort study of community-dwelling adults. The cohort was established between 1972 and 1974, when 82% of the adult residents of a southern California suburb participated in a survey of heart disease risk factors. Detailed methods of the study have been described previously [8,15,16]. Between 1984 and 1987, 80% (2,480 of 3,100) of the surviving members of the cohort participated in a diabetes epidemiology study visit (Visit 4). For the current analyses, we included the 72% of these participants who had FPG, 2hPG, and GHb measurements during Visit 4 (1,774 of 2,480 participants). The Rancho Bernardo Study was approved by the Institutional Review Board of the University of California, San Diego.

MATERIALS AND METHODS

Data Collection

Data collected at the 1984–1987 (Visit 4) clinical examination and at subsequent visits in 1992–1996 (Visit 7) and 1997–1998 (Visit 8) included demographic information, health related behaviors, medical history, and medication use. Those who reported a history of myocardial infarction, coronary revascularization, angina, stroke, transient ischemic attack, or peripheral vascular disease were classified as having pre-existing cardiovascular disease. Participants were asked about their frequency of alcohol use and were classified into those who drank alcohol daily, weekly, monthly, or less than monthly. Tobacco use was queried and participants were divided into current vs. former or never smokers.

Weight and height were measured using standard protocols with participants wearing light clothing without shoes. Waist circumference was measured at the level of the iliac crest. Two systolic and diastolic blood pressure measurements were taken using a mercury sphygmomanometer after the participant was seated for at least 5 minutes. We used the mean

of the two measurements for systolic and diastolic blood pressure. Participants were also asked whether they had been diagnosed with hypertension in the past. Hypertension was defined as self-report, use of an antihypertensive medication, systolic blood pressure ≥ 140 , or diastolic blood pressure ≥ 90 . Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Physical activity was obtained by self-report by asking whether the participant currently exercised three or more times per week.

Biological Variables

Blood was obtained by venipuncture in the morning after a requested 12-hour fast and 2 hours later after a 75 gram oral glucose load. Plasma glucose was analyzed by a glucose oxidase method. Total cholesterol and triglycerides were measured by enzymatic methods using the ABA-200 biochromatic analyzer (Abbot Laboratories, Abbot Park, IL). High-density cholesterol (HDL) was determined by precipitation analysis using a protocol from the Lipid Research Clinic. Low-density cholesterol (LDL) was calculated with the Friedewald Formula [17]. Total glycohemoglobin was analyzed by high-performance liquid chromatography. This technique measures the total amount of hemoglobin that has been modified by the non-enzymatic addition of glucose, the majority of which is hemoglobin A1c. These assays were conducted in the early 1980s before the widespread use of hemoglobin A1c for monitoring glucose control [18]. Although total glycohemoglobin and HbA1c are not identical, they are closely correlated and provide similar clinical information. Currently, hemoglobin A1c is the standard method for measuring long-term glycemic control [19]. Diabetes was defined by history (queried as a physician's diagnosis of diabetes) and/or by fasting plasma glucose level of ≥ 126 mg/dL, or a 2-hour post-glucose challenge of ≥ 200 mg/dL at the 1984–1987 clinic examination.

Mortality Data

Vital status was determined for 97% of the original cohort by annual mailings to households and was confirmed by review of the death certificates. Mortality data from the National Death Index was updated through December 31, 2002 for all 1,774 participants. Underlying cause of death was coded by a certified nosologist using the ninth revision of the International Classification of Diseases, Adapted. For this analysis, CHD mortality included underlying cause of death assigned codes between 410 and 414. The average amount of follow-up time for all participants was 13.5 ± 5.1 years. For those who died ($n=854$), it was an average of 9.6 ± 5.0 years.

Statistical Analysis

Visit 4 was considered baseline as glucose measurements were conducted at this visit. Differences in baseline characteristics for survivors versus those who died during the follow-up period were compared using t tests for continuous variables and Wilcoxon or χ^2 tests for dichotomous variables. Multivariate Cox regression models were used to examine the association between each of the three glucose measures and total mortality. We also developed multivariate Cox models with each glucose measure collected at Visit 4 to examine associations with total or CHD mortality over three time periods (0–6 years, 7–12 years, and 13–18 years of follow-up since Visit 4). All models were adjusted for potential confounding baseline cardiac risk factors, including age, sex, systolic blood pressure, diastolic blood pressure, LDL-cholesterol, current smoking, exercise ≥ 3 times per week, and aspirin use. To examine the role of potential mediators of the association between glucose and mortality, we constructed staged multivariate Cox models adjusting first for the potential confounders described above, and then adding potential mediators (waist circumference, HDL-cholesterol, triglycerides, and BMI).

To determine how to appropriately model the association of glucose measures with mortality outcomes, generalized additive models (GAMs) with a cubic B-spline function were employed

to construct splines [20]. GAMs extend the generalized linear model by allowing fit of nonparametric functions to estimate the associations of predictors and outcomes. If a spline appeared to have quadratic or non-linear properties, a quadratic term was added to the model and the significance of that term was assessed. Using these methods, we determined that the association of the glycemic measures with mortality was approximately linear without threshold effects.

Separate analyses were conducted stratifying by sex and excluding the 67 (4%) of subjects who had diabetes at the 1984–1987 visit based on reported history and/or FPG or 2hPG results. To examine secular trends, we compared the prevalence of health behaviors and use of aspirin, lipid-lowering medications, blood pressure medications (diuretics, beta blockers, and calcium channel blockers), and menopausal hormone therapy (estrogen with or without progestin) during each visit.

SPlus Version 6.1 (Insightful Corp, Seattle, WA) was used for splines and for testing of the proportional hazards assumption; SAS Version 9.1 (Cary, NC) was used for all other analyses. The global and individual variable proportional hazards assumptions were verified by examining plots of Schoenfeld residuals versus transformed time and by assessing interactions of the glucose predictors and other potential confounders with time. All tests showed $p > 0.05$, indicating that the proportional hazards assumption was met for all individual variables in each model and the overall model. With a power of 0.80, Type 1 error rate of 0.05, and the standard deviations for the glycemic values that we observed, we could detect HRs of at least 1.12 for GHb, 1.05 for FPG, and 1.02 for 2hPG glucose.

RESULTS

The characteristics of the study participants are shown in Table 1. The median age of participants was 68 years. At the end of a maximum 18-year follow-up, 854 (48%) participants had died. The total number of deaths during the follow-up intervals was 227 (13%) in years 0–6, 330 (21%) in years 7–12, and 297 (24%) in years 13–18. The mean age at death in the time periods was 80.9(± 7.9) in years 0–6, 84.7 (± 8.3) in years 7–12, and 86.7 (± 7.7) in years 13–18 (p for trend=0.002). Those who died had a greater prevalence of diabetes ($p=0.002$) and hypertension ($p<0.001$) at baseline.

Causes of mortality

Over the total follow-up period, 182 (21%) of the deaths were attributed to CHD. The proportion of deaths due to CHD did not differ significantly over the three time intervals- 69 (30%) occurred in years 0–6, 63 (19%) occurred in years 7–12, and 50 (17%) occurred in years 13–18 ($p=0.21$). The distribution of causes of death was similar in men and women.

Glycemic measures and mortality

Spline analyses showed approximately linear associations between the glycemic measures and mortality with no threshold effects. Unadjusted associations of the three measures and total mortality are shown in Table 1. Baseline GHb and 2hPG were significantly higher in those who died than in survivors ($P<0.001$ for both measures), with a non-significant trend towards higher fasting plasma glucose levels in those who died ($p=0.07$). After adjustment for age, sex, systolic and diastolic blood pressure, LDL-cholesterol, physical activity, and aspirin use, only glycohemoglobin was a significant predictor of total mortality over the full follow-up period. Each percentage point increase in GHb was associated with an 11% increase in hazard for total mortality (95% CI + 3 to +20%, $p=0.007$). The hazard ratios for total mortality were 1.01 (95% CI 1.00–1.03, $p=0.09$) for each 10 mg/dL increase in 2hPG and 1.02 (95% CI 0.99–1.06, $p=0.20$) for each 10 mg/dL increase in FPG. In similarly adjusted analyses, none of the three

glycemic measures were significantly associated with CHD mortality during the full follow-up period, with hazard ratios of 1.15 (95% CI 0.99–1.34, $p=0.08$) for GHb, 1.01 (0.98–1.04, $p=0.50$) for 2hPG, and 1.03 (0.97–1.10, $p=0.30$) for FPG.

Effect of follow-up interval on associations with mortality

The associations between glycemic measures and mortality varied with time since measurement (Figure 1). In adjusted models, GHb was a significant predictor of both total and CHD mortality during years 0–6 ($p=0.04$ for total mortality, $p=0.02$ for CHD mortality), but not during years 7–12 and 13–18 of follow-up. Neither 2hPG nor FPG were independent predictors of total or CHD mortality during these time periods (Figure 1).

Effect of potential confounders and mediators

The significant association between GHb and total and CHD mortality during the first 6 years persisted after adjustment for age and other cardiac risk factors (Table 2). Further adjustment for variables that may lie in the causal pathway between GHb and CHD mortality (waist circumference, HDL-cholesterol, triglycerides, and BMI) did not substantially attenuate these associations (for total mortality HR 1.11, 95% CI 0.97–1.27, $p=0.13$; for CHD mortality HR 1.22, 95% CI 0.98–1.51, $p=0.08$). In models adjusted sequentially for each confounder, age and triglycerides attenuated the association between GHb and CHD mortality more than the other covariates. For the association between GHb and total mortality, age, aspirin use, and exercise had the greatest attenuating effect.

Effect of sex and diabetes

In sex-stratified adjusted models, the association of GHb with total and cardiovascular mortality was similar for men and women. Exclusion of the 67 (4%) participants with diabetes at baseline did not substantially change the results.

Secular trends

Table 3 shows changes in use of medications and in health behaviors over time. Use of aspirin and statins increased over time. Use of blood pressure medications decreased over time. This may be due to the increasing use of medications, such as ACE inhibitors, which were introduced during the study period but not included in this analysis. Regular exercise and smoking also decreased over time. Table 4 shows the proportion of surviving participants who newly started and stopped aspirin, statins, and blood pressure medications during the course of the study. Between visits, more patients started rather than discontinued these medications.

DISCUSSION

In this study of older men and women with measures of glycohemoglobin, 2-hour post-challenge glucose, and fasting glucose, only glycohemoglobin was a significant predictor of overall mortality independent of age and other cardiac risk factors. To our knowledge, this is the first study to examine how the predictive value of glycemic measures change with time since measurement. In these time-stratified analyses, only baseline GHb was significantly associated with total and CHD mortality and only during years 0–6. Our findings did not differ by sex, were not changed by the exclusion of participants with known diabetes, and were present throughout the range of GHb without any threshold effects.

Our results expand upon prior work showing that GHb predicts CHD events and mortality at levels lower than those currently considered to be diagnostic of impaired glucose tolerance or diabetes [3,8,13]. Prior studies in this area have had conflicting results and few studies have been able to compare multiple glycemic measures in the same subjects [12]. The Framingham

Offspring Study of 3,370 men and women did compare fasting glucose, post-challenge glucose, and HbA1c [7]. Though all were significant predictors of incident cardiovascular disease events over a 4-year follow-up period, when modeled together, only post-challenge glucose remained a significant independent predictor. It is not clear why post-challenge glucose did not predict CHD or total mortality in our study population. Even in research settings, oral glucose tolerance tests have shown poor reproducibility, with most estimates near 60%, and this could have obscured an association with mortality [21]. Glycohemoglobin may also be a more integrative measure of typical blood glucose levels as it reflects both fasting and postprandial glucose and provides an estimate of glycemic control over 4–12 weeks.

In addition to comparing the associations of glycemic measures with mortality, we also examined how these associations changed over time. Our finding that GHb was a significant predictor of mortality only in the first 6 years of follow-up could be explained by a healthy survivor bias or by secular trends in health care. Over the study period, increasing rates of overweight and obesity in the United States led to an emphasis on improving diet and exercise [22]. Study participants were relatively affluent and well-educated, and were informed of the baseline (1984–1987) glucose, lipids, and blood pressure results. They may have been more likely to adopt healthier lifestyles, and these secular trends may have reduced mortality in the study population [23]. In support of this possibility, we found that smoking rates decreased and use of cardioprotective medications increased over time in study participants. However, we do not have detailed medical record data and can be certain of the indications for medication use or their efficacy in lowering cardiovascular risk factor levels.

The mechanisms behind our findings linking higher glycohemoglobin to increased CVD and mortality in people without diabetes remain unclear, but this is an area of active research. Sasso and colleagues recently evaluated glucose metabolism in 234 men with normal glucose tolerance referred for coronary angiography. They found HbA1c and post-challenge glucose were significantly higher in those with more severe atherosclerosis. Poorer glycemic and insulin resistance measures were also independently associated with a greater number of stenosed vessels [24]. The biologic pathway behind these changes may involve increased production of advanced glycation end products (AGEs), which have been found in atherosclerotic plaques in adults with and without diabetes [25]. Hyperglycemia increases the production of AGEs, and these molecules are associated with increased oxidative stress, inflammation, and endothelial damage that could accelerate atherosclerosis [26].

Strengths of our study include the long follow-up, simultaneous measures of 3 glycemic variables, and quality measures of classical confounding and mediating variables. The participants in this study include those who chose to attend Visit 4 and who had all 3 glucose measures, which may not be representative of the entire initial cohort. The largely Caucasian and middle- to upper-middle class older adult cohort limits generalizability, but reduces unmeasured confounding due to socioeconomic status. Though we adjusted for cardiac risk factors and examined changes medications and health behaviors over time, there may be additional unaccounted factors which influenced mortality risk. In addition, the smaller number of CHD deaths may have limited our power to find significant associations between the glucose measures and CHD mortality. Finally, because our goal was to evaluate the association of a single time point glycemic measurement with time to mortality, we did not examine the predictive value of repeated glycemic measures over time.

In summary, in this prospective study of 1,774 community dwelling adults, baseline glycohemoglobin was a significant predictor of total mortality while fasting and post-challenge glucose were not significantly associated with mortality after adjustment for traditional cardiac risk factors. This association was sensitive to follow-up time, with GHb predicting total and CHD mortality in years 0–6 but not in years 7–12 or 13–18. This waning effect of

hyperglycemia on mortality with time may be due to a healthy survivor bias or to secular trends in medication use and health behaviors. Our findings in a relatively healthy population without diabetes support the hypothesis that early glycemic control may affect mortality outcomes. However, though GHb can predict total and CHD mortality in people without diabetes, no trials have shown that improving glucose metabolism will reduce CHD or total mortality. Therefore, further research is needed to understand how the observed association between glycohemoglobin and early mortality should be applied to improve clinical outcomes.

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Figure 1. Adjusted association of glycemic measures with total and CHD mortality over time
Models adjusted for age, sex, systolic bp, diastolic bp, LDL, smoking, exercise, aspirin use.

Table 1

Baseline (1984–1987) characteristics by vital status (18 years follow-up)

	Total mortality n=854	Alive n=920	p-value
Median age (IQR), y	76 (70–81)	62 (55–68)	0.64
Male, %	50.7	38.6	<0.001
Current smoker, %	15.1	16.4	0.44
Exercise ≥ 3 x/week, %	79.2	83.0	0.03
Mean BMI, <i>kg/m²</i>	24.7 (3.7)	25.1 (3.6)	0.02
Mean Waist circumference (SD), <i>cm</i>	86.3 (12.0)	83.4 (12.1)	0.76
Cardiovascular disease, %	255 (30)	113 (12)	<0.0001
Hypertension, %	75.5	48.9	<0.0001
Diabetes, %	5.3	1.7	0.002
Mean LDL (SD), <i>mg/dl</i>	134 (39)	136 (36)	0.15
Mean HDL (SD), <i>mg/dl</i>	61 (19)	63 (19)	0.009
Mean Triglycerides (SD), <i>mg/dl</i>	117 (76)	118 (84)	0.63
Aspirin, %	21.6	17.2	0.02
Lipid-lowering medication, %	1.8	1.0	0.22
Blood pressure medication, %	39.6	23.9	<0.0001
Mean glycohemoglobin (SD), %	6.2 (1.0)	6.0 (0.9)	<0.001
Mean fasting glucose (SD), <i>mg/dl</i>	101 (21)	100 (18)	0.07
Mean 2-hr PC [*] glucose (SD), <i>mg/dl</i>	146 (60)	126 (45)	<0.001
Alcohol Use [†]			
<monthly, %	12.9	11.4	
monthly/weekly, %	30.0	35.2	0.14
Daily, %	44.0	43.6	

* PC = postchallenge

[†] n=90 missing from alive group, n=112 missing from mortality group

Table 2

Association of glycohemoglobin and mortality over different follow-up time periods

	0–6 years			7–12 years			13–18 years		
	Died	Survived		Died	Survived		Died	Survived	
n (%)	227	1547		330	1217		297	920	
Mean age at beginning of interval:	77.6 ± 7.7	66.5 ± 11.1		82.7 ± 8.4	71.1 ± 10.4		84.5 ± 7.5	74.6 ± 10.1	
Baseline GHb (%):	6.4 ± 1.1	6.1 ± 0.9		6.4 ± 1.1	6.0 ± 0.9		6.2 ± 0.9	6.0 ± 0.9	
Total Mortality:	HR (95% CI) *	p-value		HR (95% CI) *	p-value		HR (95% CI) *	p-value	
Unadjusted	1.26 (1.14–1.39)	<0.001		1.18 (1.07–1.30)	<0.001		1.15 (1.03–1.29)	0.01	
Age-adjusted *	1.14 (1.01–1.30)	0.04		1.08 (0.95–1.21)	0.24		1.07 (0.94–1.23)	0.32	
Fully adjusted	1.14 (1.01–1.30)	0.04		1.09 (0.96–1.23)	0.19		1.11 (0.96–1.27)	0.15	
CHD Mortality:									
Unadjusted	1.35 (1.15–1.57)	<0.001		1.12 (0.88–1.43)	0.37		1.21 (0.95–1.54)	0.12	
Age-adjusted *	1.24 (1.02–1.51)	0.03		0.96 (0.71–1.30)	0.80		1.14 (0.84–1.55)	0.41	
Fully adjusted	1.26 (1.03–1.55)	0.02		0.97 (0.71–1.31)	0.83		1.16 (0.86–1.31)	0.33	

* Adjusted for age, sex, systolic bp, diastolic bp, smoking, LDL, exercise, aspirin use

Table 3

Secular trends in medication use, alcohol, smoking, and exercise over the study period

	Visit 4 1984–1987 N=1774	Visit 7 1992–1996 N=1315	Visit 8 1997–1999 N=1127
Aspirin use	21.5%	33.8%	36.8%
Statin use	0.7%	10.3%	19.4%
Blood pressure medication use	31.5%	23.4%	21.5%
Hormone therapy use (women)	14.8%	38.9%	43.5%
Daily alcohol use	42.9%	44.5%	46.8%
Current smoker	12.3%	7.9%	5.8%
Exercise 3x/wk	81.0%	70.1%	74.2%

Table 4

Changes in medication use over the study period

	Visit 4 to 7 N=855 n (%)	Visit 7 to 8 N=535 n (%)
Aspirin		
started	197 (23.0%)	83 (15.5%)
discontinued	62 (7.3%)	68 (12.7%)
Lipid-lowering medication		
started	79 (9.2%)	51 (9.5%)
discontinued	2 (0.2%)	11 (2.1%)
Blood pressure medication		
started	121 (14.1%)	80 (14.9%)
discontinued	51 (5.9%)	16 (3.0%)