Effect of Glycemia on Mortality in Pima Indians With Type 2 Diabetes

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The effect of plasma glucose concentration on overall and cause-specific mortality was examined in 1,745 Pima Indians (725 men, 1,020 women) ≥15 years old with type 2 diabetes. During a median follow-up of 10.6 years (range 0.1–24.8), 533 subjects (275 men, 258 women) died; 113 of the deaths were attributable to cardiovascular disease, 96 to diabetes-related diseases (diabetic nephropathy for 92 of these), 249 to other natural causes, and 75 to external causes. After adjusting for age, sex, duration of diabetes, and BMI in a generalized additive proportional hazards model, higher baseline 2-h postload plasma glucose concentration predicted deaths from cardiovascular disease (P = 0.007) and diabetes-related diseases (P = 0.003), but not from other natural causes (P = 0.73). An increment of 5.6 mmol/l (100 mg/dl) in the 2-h plasma glucose concentration was associated with 1.2 times (95% CI 1.1–1.4) the death rate from cardiovascular disease, 1.3 times (95% CI 1.1–1.5) the death rate from diabetes-related diseases, and almost no change in the death rate from other natural causes (rate ratio = 1.0; 95% CI 0.94–1.1). In Pima Indians with type 2 diabetes, higher plasma glucose concentration predicts deaths from cardiovascular and diabetes-related diseases but has little or no effect on deaths from other natural or external causes. ***Diabetes*** **48:896–902, 1999**

Cardiovascular and renal disease are primarily responsible for the higher death rates in people with diabetes (1–5). Risk factors for these complications include high blood pressure, hyperinsulinemia, albuminuria, and serum lipid and lipoprotein abnormalities (1–4,6–9). Each of these factors is influenced by the prevailing blood glucose concentration (10–16), which suggests that death rates from these complications may be higher in diabetic patients with more severe hyperglycemia. Although the effect of hyperglycemia on microvascular disease is well established (17), its effect on cardiovascular disease is less certain. The World Health Organization Multinational Study (6) found little association between glucose and cardiovascular disease in nine different diabetic populations, and the Framingham Study reported that glycated hemoglobin was related to cardiovascular disease prevalence only in women (18). More recently, however, several prospective studies found positive relationships between glycemic level and cardiovascular mortality (7,8,19–22), and one study reported a positive relationship with other natural causes of death (23).

In Pima Indians, as in other populations, diabetes adversely affects mortality, and nearly all of the excess deaths among those with diabetes are attributable to renal and coronary heart disease (5). In this study, we examined the effect of glucose on overall and cause-specific mortality in Pima Indians with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Pima and the closely related Tohono O'odham Indians from the Gila River Indian Community participate in a longitudinal diabetes study (24). Since 1965, each member of the community ≥5 years of age is asked to have a research examination every 2 years. A recent study found that 85% of community members had participated in these examinations (25), which include a glucose tolerance test with determination of the glucose concentration in venous plasma drawn 2 h after a 75-g oral carbohydrate load. A fasting glucose measurement was added in July 1975, and glycated hemoglobin was added in June 1983. Because neither of these measurements was made consistently throughout the entire study period, their effects were not estimated. Diabetes was defined according to the criteria of the World Health Organization (26). The date of diagnosis was determined from the research examinations, or from review of clinical records if diabetes had been diagnosed in the course of routine medical care.

Between 1 January 1965 and 31 December 1989, 5,506 people who were at least half-Pima or half–Tohono O'odham resided in the community and had one or more research examinations after 15 years of age. The study population comprised the 1,745 subjects with type 2 diabetes; 30 subjects with missing data were excluded. Each subject's vital status as of 31 December 1989 was determined. For all deaths, the accuracy and completeness of the underlying and contributory causes reported on death certificates were assessed by review of clinical records and reports of autopsy and medical examiner findings as described previously (5,27). The adjudicated causes were coded in accordance with guidelines of the National Center for Health Statistics (28–32). Terminology and codes of the *International Classification of Disease, Ninth Revision* (ICD-9) (33) were used for recording causes of death and other diagnoses. Deaths were considered "natural" if they were due to disease (ICD-9 codes 001.0–799.9) and "external" if they were due to injury or poisoning (ICD-9 codes 800.0–999.9).

Statistical analysis. Death rates were calculated as the number of subjects who died divided by the person-years of follow-up and expressed per 1,000 per year. The period of risk extended from the date of the first examination after the onset of diabetes to death or to 31 December 1989. Death rates were examined according to quartiles of baseline 2-h postload plasma glucose concentration and were standardized to the 1980 Pima Indian population.

The effect of 2-h postload plasma glucose concentration on mortality was examined by using a generalized additive Cox proportional hazards model to control for the effects of potentially confounding variables. These variables included age, sex, duration of diabetes, and BMI. The generalized additive model relaxes the linearity assumptions of the conventional regression model and allows smooth nonlinear functions of the covariates to be included in the log hazard ratio (34,35). This feature permits the dose-response relationship between glucose and mortality to be examined more accurately than by standard categorical analysis, which may not adequately describe the trends in the data and does not make efficient use of within-category information (36). Smoothed terms were used for glucose concentration and for duration of diabetes in some models but not for age or BMI, because inspection of additive function plots and statistical testing

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ICD-9, *International Classification of Diseases, Ninth Revision*.

of the nonlinearity of effect suggested that only glucose and duration had important non–log-linear associations with the outcome. Continuous variables included in the regression models were centered at their mean baseline values. The effects of time-dependent variables were assessed at baseline and at each subsequent examination. If the values changed, the new values were included for the appropriate time periods. Product terms of predictor variables did not improve the regression models and were not included.

RESULTS

Of 1,745 diabetic subjects (725 men, 1,020 women) ≥15 years of age, 533 (275 men, 258 women) died during a median follow-up of 10.6 years (range 0.1–24.8). Clinical and demographic features of the study population are shown in Table 1. Death rates were higher in men than in women and rose with increasing age (Table 2). Age- and sex-adjusted all-cause mortality according to quartiles of baseline 2-h postload plasma glucose concentration is shown in Fig. 1. Higher glucose concentrations were generally associated with higher death rates.

Of the 533 deaths, 113 were due to cardiovascular disease, 96 to diabetes-related diseases, 249 to other natural causes, and 75 to external causes (Table 3). Of the subjects who died from cardiovascular disease, 42% (47 of 113) had proteinuria (protein-to-creatinine ratio ≥0.5 g/g) at their last examination, and 23% (26 of 113) also had renal insufficiency (serum creatinine ≥177 μmol/l [2.0 mg/dl]). Of the deaths attributed to cardiovascular disease, 64% (72 of 113) were due to ischemic heart disease, 25% (28 of 113) to stroke, and 12% (13 of 113) to other causes (4 to unspecified cardiovascular disease, 3 to subarachnoid hemorrhage, 3 to valvular disease, 1 to endocarditis, 1 to pulmonary embolism, and 1 to late effects of cerebrovascular disease). Of the 96 deaths attributed to diabetes-related diseases, 92 (96%) were due to diabetic nephropathy, and 4 (4%) to other causes (2 to diabetes with peripheral circulatory disorders, 1 to hyperosmolar coma, and 1 to craniofacial mucormycosis). Of the 249 deaths attributed to other natural causes, 67 (27%) were due to infections, 55 (22%) to malignant neoplasms, 45 (18%) to alcoholic liver disease, and 82 (33%) to other causes (32 to unattended, ill-defined, or unknown causes of death; 7 to acute alcohol intoxication; 11 to acute cholecystitis or ascending cholangitis; 3 to aspiration pneumonia; 3 to acute pancreatitis; and 26 to various other causes). The leading causes of death were ischemic heart disease in the men and diabetic nephropathy in the women.

TABLE 1
Baseline clinical and demographic features of 1,745 diabetic Pima Indians (725 men, 1,020 women)

	Mean ± SD	Range
Age (years)	43 ± 15	15–88
Duration of diabetes (years)	2.5 ± 4.6	0–37.9
BMI (kg/m^2)		
Men	32.0 ± 6.8	12.0–84.4
Women	34.7 ± 7.2	19.9–72.6
2-h plasma glucose (mmol/l)	18.5 ± 7.2	4.1–63.8
Mean arterial pressure (mmHg)	99 ± 15	51–189
Serum cholesterol (mmol/l)	4.8 ± 1.1	2.0–10.9

Data were missing for mean arterial pressure in 66 subjects and for serum cholesterol concentration in 52 subjects.

Age- and sex-adjusted death rates from cardiovascular disease, diabetes-related diseases, and other natural causes according to quartiles of 2-h postload plasma glucose concentration are shown in Fig. 2. In general, higher plasma glucose concentrations were associated with higher death rates from cardiovascular disease and diabetes-related diseases, but not with death rates from other natural causes of death. No relationship with plasma glucose was found for external causes of death (data not shown).

When examined as a smoothed continuous variable in a generalized additive proportional hazards model, the higher baseline 2-h postload plasma glucose concentration was associated with cardiovascular (P = 0.007) and diabetes-related deaths (P = 0.003), but not with other natural causes of death (P = 0.73), when adjusted for age, sex, duration of diabetes, and BMI (Fig. 3). For cardiovascular mortality, the dose-response effect of glucose was modestly non–log-linear (P = 0.11 when tested for nonlinearity), with the risk of death not rising further for baseline glucose concentrations >30 mmol/l (540 mg/dl). In the range of glucose values for most patients, however, an increment of 5.6 mmol/l (100 mg/dl) in the plasma glucose concentration was associated with 1.2 times (95% CI 1.1–1.4) the death rate from cardiovascular disease; the effect was greater in subjects with proteinuria (death rate ratio = 1.3; 95% CI 1.1–1.7) than in those without proteinuria (death rate ratio = 1.1; 95% CI 0.92–1.4). The same increment in the plasma glucose concentration was associated with 1.3 times (95% CI 1.1–1.5) the death rate from diabetes-related diseases and

TABLE 2
Number of deaths and death rates, by age and sex, in 1,745 diabetic Pima Indians

	Men			Women		
Age (years)	Deaths (n)	Person-years	Death rate (per 1,000 years)	Deaths (n)	Person-years	Death rate (per 1,000/year)
15–24	2	254.8	7.8	2	374.6	5.3
25–34	15	1,041.7	14	9	1,519.1	5.9
35–44	22	1,891.0	12	23	2,537.2	9.1
45–54	57	1,840.5	31	41	3,033.1	14
55–64	52	1,213.9	43	59	2,541.6	23
65–74	52	896.1	58	69	1,488.0	46
≥75	75	485.1	155	55	618.9	89
Total	275	7,623.1	36	258	12,112.5	21

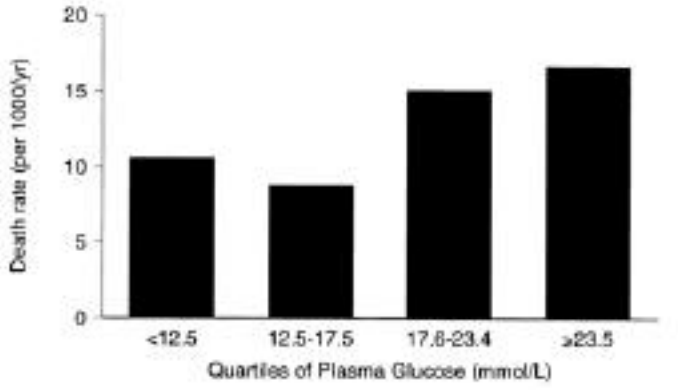

FIG. 1. Age- and sex-adjusted death rates (per 1,000/year) for all natural causes of death in Pima Indians according to quartiles of 2-h postload plasma glucose concentration at baseline.

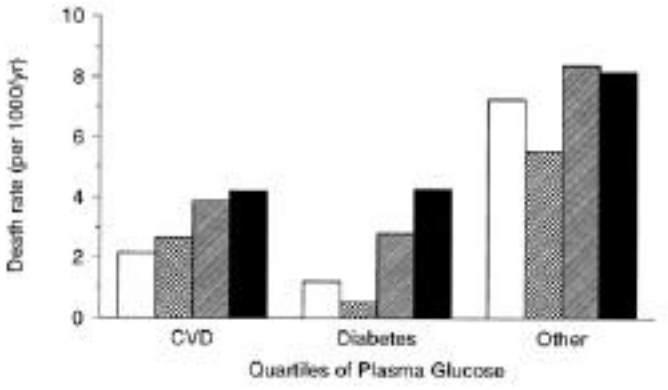

FIG. 2. Age- and sex-adjusted death rates (per 1,000/year) in Pima Indians according to quartiles of 2-h postload plasma glucose concentration at baseline. Rates are shown for cardiovascular disease (CVD), diabetes-related diseases, and other natural causes of death. Quartiles of plasma glucose (in mmol/l) are <12.5 □, 12.5–17.5 ▦, 17.6–23.4 ▨, and ≥23.5 ■.

almost no change in the death rate from other natural causes (rate ratio = 1.0; 95% CI 0.94–1.1) (Table 4). Inclusion of blood pressure and cholesterol in the models (Table 5) reduced the effect of plasma glucose concentration on deaths from cardiovascular disease but did not affect deaths from diabetes-related diseases or other natural causes. The 2-h postload plasma glucose concentration did not affect deaths from external causes (data not shown).

Older age strongly predicted all natural causes of death in both sexes, but men were more likely than women to die of cardiovascular or other natural causes of death unrelated to diabetes (Table 4). By contrast, diabetes-related deaths occurred at about the same rate in men and women. Duration of diabetes was a risk factor for cardiovascular and diabetes-related diseases but not for other natural causes of death (Table 4).

In analyses that accounted for time-dependent changes in covariate values, the effect of 2-h post-load plasma glucose concentration remained monotonic for cardiovascular disease (i.e., higher death rates were associated with higher glucose concentrations), but was U-shaped for diabetes-related diseases ($P < 0.001$ when tested for nonlinearity) (Fig. 4). Glucose concentration had no effect on other natural causes of death (Fig. 4) or on external causes of death in the time-dependent analysis (data not shown).

DISCUSSION

In Pima Indians with type 2 diabetes, higher plasma glucose concentration at baseline predicted deaths from cardiovascular and diabetes-related disease. These results are consistent with those found in Caucasian populations from Finland (7,8,20), Sweden (19), Wisconsin (21), and Texas (22). All but 4 (96%) of the deaths from diabetes-related diseases were due to diabetic renal disease, confirming the importance of glycemia as a risk factor for renal disease in this population. By contrast, the glucose concentration had no important effect on other natural causes of death or on external causes, such as homicide or automobile accidents. Even deaths from infectious diseases, which are strongly related to the duration of diabetes in this population (5), were not affected by the glucose concentration. Because most of the excess deaths associated with diabetes were attributable to cardiovascular and

TABLE 3
Number of deaths and death rates from underlying causes of death in 1,745 diabetic Pima Indians

Underlying cause of death (ICD-9 codes)	Men		Women		Both sexes	
	Deaths (*n*)	Death rate (per 1,000/year)*	Deaths (*n*)	Death rate (per 1,000/year)*	Deaths (*n*)	Death rate (per 1,000/year)*
Cardiovascular disease (390.0–459.9)	63	4.1	50	2.2	113	3.1
Ischemic heart disease (410.0–414.9)	49	3.1	23	1.0	72	2.0
Stroke (431.0–434.9, 436)	11	0.70	17	0.68	28	0.67
Other cardiovascular diseases	3	0.21	10	0.50	13	0.37
Diabetes-related diseases (250.0–250.9)	33	2.1	63	2.4	96	2.2
Diabetic nephropathy (250.4)	31	2.0	61	2.3	92	2.1
Other diabetes-related diseases	2	0.13	2	0.09	4	0.11
Other natural causes	133	9.5	116	5.0	249	7.3
Infections†	24	1.9	43	1.8	67	1.9
Malignant neoplasms (140.0–208.9)	23	1.5	32	1.3	55	1.4
Alcoholic liver disease (571.0–571.3)	30	2.0	15	0.58	45	1.3
Other causes	56	4.2	26	1.4	82	2.8
All external causes (E800–E999)	46	7.2	29	3.7	75	5.4
All causes	275	23	258	13	533	18

*Data are age-adjusted for each sex and are age- and sex-adjusted for both sexes combined. †ICD-9 codes for infections are 001.0–139.8, 320.0–326.9, 460.0–466.1, 480.0–487.8, 540.0–543.9, 572.0, 590.0–590.9, 599.0, 680.0–686.9, and 729.4.

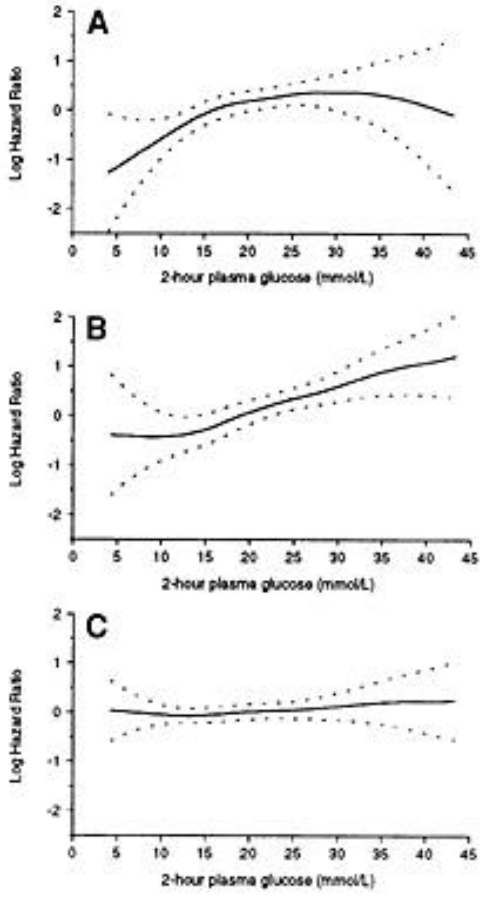

FIG. 3. Function plots for the effect of 2-h postload plasma glucose concentration on cardiovascular disease (*A*), diabetes-related diseases (*B*), and other natural causes of death (*C*), adjusted for age, sex, duration of diabetes, and BMI. The effects are estimated from baseline measurements. The curves are centered to have an average of zero over the range of the data. Approximate pointwise 95% CIs are indicated (– – –). The graphs were truncated at a glucose concentration of 45 mmol/l because only four baseline observations were above that level.

renal disease (5,7,8,19–23), it is not surprising that other natural causes of death would not be affected greatly by the level of glycemia. Burke et al. (23) did report a significant effect of glucose on other natural causes, but their study was very small, with only 27 such deaths.

The finding that 42% of the subjects who died from cardiovascular disease had coincident nephropathy is consistent with the widely held belief that renal and cardiovascular disease are both manifestations of a generalized vascular disorder associated with diabetes (37). The present study suggests that the effect of hyperglycemia on deaths from cardiovascular disease operates principally through this generalized disorder, because hyperglycemia did not predict cardiovascular deaths in subjects without proteinuria. Hyperglycemia may promote a generalized vascular disorder by raising blood pressure (10,11), worsening insulin resistance and hyperinsulinemia (12), glycating proteins in the walls of arteries (13), and accelerating thrombus formation (14) and oxidation of lipoproteins (15), but the proportion of deaths attributed to either cardiovascular or renal disease is determined in part by the age at onset of diabetes and by the underlying susceptibility to these diseases. Until recently, deaths from ischemic heart disease were relatively uncommon in Pima Indians, suggesting that racial heritage, low serum concentrations of total and LDL cholesterol, and the rarity of heavy smoking protected this population from cardiovascular disease (25,38). The recent rise in deaths from ischemic heart disease among Pima Indians with diabetes coincides with dramatic improvements in survival among the Indians treated with dialysis (39), suggesting that prolonging survival after the onset of end-stage renal disease has, at least in part, increased the likelihood of developing fatal ischemic heart disease in this population (25,40).

Previous studies of the effect of glucose on mortality were often based on a single measurement at the start of follow-up. Because metabolic control in type 2 diabetes frequently deteriorates over time (41), this method may underestimate the harmful effect of hyperglycemia. For this reason, the present study also included an analysis of glucose values at each research examination. In this time-dependent analysis, the effect of glucose on deaths from cardiovascular disease was equivalent to the analysis of the baseline data, but the effect on deaths from renal disease was U-shaped, indicating that lower as well as higher glucose concentrations predicted deaths from this disease. This finding should not be taken to suggest that careful regulation of blood sugar is unwarranted or even damaging to the kidney. Rather, the lower plasma glucose concentration probably modifies insulin action, ambient insulin levels, and insulin sensitivity, because uremia affects the metabolism of certain hormones, including glucagon, and it also alters hormone-receptor function. Indeed, 74% of the subjects

TABLE 4
Estimated adjusted effects (rate ratios and 95% CIs) of 2-h postload plasma glucose concentration and other factors measured at baseline on deaths from cardiovascular disease, diabetes-related diseases, and other natural causes in 1,745 diabetic Pima Indians: results of generalized additive proportional-hazards regression analysis

Model covariates	Rate ratio (95% CI)	*P* value
Cardiovascular disease (113 deaths)		
Age (per 10 years)	2.1 (1.8–2.5)	<0.001
Sex (M/F)	2.1 (1.5–3.1)	<0.001
Duration of diabetes (per 10 years)	1.6 (1.2–2.0)	0.001
BMI (per 5 kg/m^2)	1.0 (0.85–1.2)	0.86
2-h plasma glucose (per 5.6 mmol/l)	1.2 (1.1–1.4)	0.007
Diabetes-related deaths (96 deaths)		
Age (per 10 years)	1.3 (1.1–1.6)	0.001
Sex (M/F)	1.1 (0.71–1.7)	0.71
BMI (per 5 kg/m^2)	1.2 (0.97–1.4)	0.10
2-h plasma glucose (per 5.6 mmol/l)	1.3 (1.1–1.5)	<0.001
Other natural causes of death (249 deaths)		
Age (per 10 years)	1.8 (1.6–1.9)	<0.001
Sex (M/F)	1.7 (1.4–2.3)	<0.001
Duration of diabetes (per 10 years)	1.2 (0.96–1.5)	0.11
BMI (per 5 kg/m^2)	0.86 (0.76–0.97)	0.01
2-h plasma glucose (per 5.6 mmol/l)	1.0 (0.94–1.1)	0.53

Rate ratios are given for the number of units shown in parentheses after model covariates and are adjusted for the other variables in the model. Because of nonlinearities in the effect of diabetes duration on diabetes-related deaths ($P < 0.001$ when tested for nonlinearity), a smoothed term was used for this variable in the regression model, and a rate ratio was not computed.

TABLE 5
Estimated adjusted effects (rate ratios and 95% CIs) of 2-h postload plasma glucose concentration and other factors measured at baseline on deaths from cardiovascular disease, diabetes-related diseases, and other natural causes in 1,660 diabetic Pima Indians: results of generalized additive proportional-hazards regression analysis, with adjustment for mean arterial pressure and serum cholesterol concentration

Model covariates	Rate ratio (95% CI)	*P* value
Cardiovascular disease (100 deaths)		
Age (per 10 years)	2.1 (1.8–2.4)	<0.001
Sex (M/F)	2.3 (1.5–3.4)	<0.001
Duration of diabetes (per 10 years)	1.6 (1.2–2.0)	<0.001
BMI (per 5 kg/m^2)	0.99 (0.82–1.2)	0.93
Serum cholesterol (per 1.3 mmol/l)	1.5 (1.2–1.8)	<0.001
2-h plasma glucose (per 5.6 mmol/l)	1.1 (0.94–1.3)	0.23
Diabetes-related deaths (84 deaths)		
Age (per 10 years)	1.2 (0.95–1.4)	0.16
Sex (M/F)	0.84 (0.53–1.3)	0.47
BMI (per 5 kg/m^2)	1.0 (0.82–1.2)	0.96
Serum cholesterol (per 1.3 mmol/l)	1.2 (0.92–1.4	0.21
2-h plasma glucose (per 5.6 mmol/l)	1.3 (1.1–1.4)	<0.001
Other natural causes of death (226 deaths)		
Age (per 10 years)	1.8 (1.6–2.0)	<0.001
Sex (M/F)	1.8 (1.4–2.3)	<0.001
Duration of diabetes (per 10 years)	1.2 (0.99–1.6)	0.06
BMI (per 5 kg/m^2)	0.86 (0.76–0.98)	0.02
Serum cholesterol (per 1.3 mmol/l)	0.84 (0.71–0.98)	0.03
2-h plasma glucose (per 5.6 mmol/l)	1.0 (0.95–1.2)	0.39

Rate ratios are given for the number of units shown in parentheses after model covariates and are adjusted for the other variables in the model. Because of nonlinearities in the effects of diabetes duration on diabetes-related deaths ($P < 0.001$ when tested for nonlinearity) and of mean arterial pressure on each cause of death ($P = 0.06$ for cardiovascular deaths, $P = 0.02$ for diabetes-related deaths, and $P = 0.02$ for other natural causes of death), smoothed terms were used for these variables in the regression models, and rate ratios were not computed. Missing data for BMI and/or serum cholesterol concentration at baseline reduced the total number of subjects by 85, cardiovascular deaths by 13, diabetes-related deaths by 12, and other natural causes of death by 23 in comparison with Table 4.

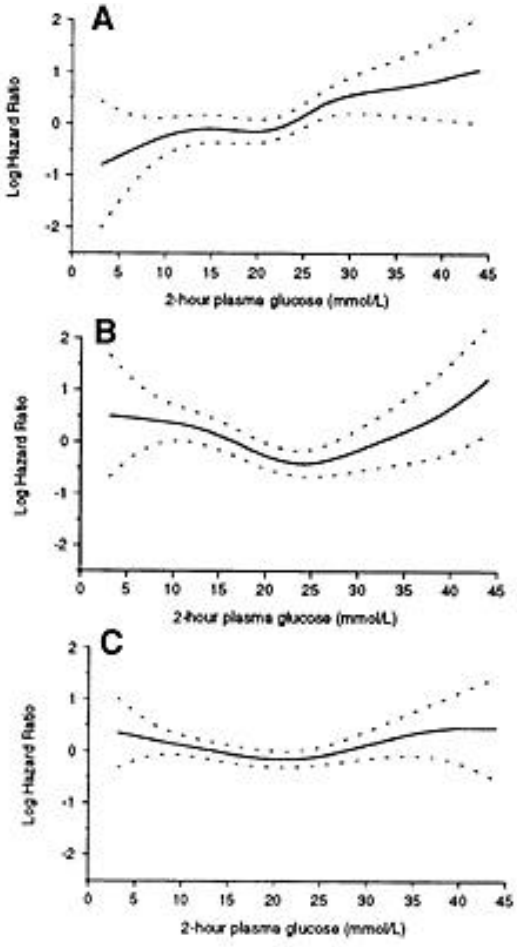

FIG. 4. Function plots for the effect of 2-h postload plasma glucose concentration on cardiovascular disease (*A*), diabetes-related diseases (*B*), and other natural causes of death (*C*), adjusted for age, sex, duration of diabetes, and BMI. The effects are estimated from time-dependent variables measured at each research examination. The curves are centered to have an average of zero over the range of the data. Approximate pointwise 95% CIs are indicated (– – –). The graphs were truncated at a glucose concentration of 45 mmol/l because only six observations were above that level.

who died from diabetes-related diseases and had glucose concentrations <15 mmol/l (270 mg/dl) at their last examination also had renal insufficiency at that examination, whereas only 31% of those with glucose concentrations ≥25 mmol/l (450 mg/dl) had renal insufficiency.

Implicit in a time-dependent analysis are the assumptions that *1*) the study exposure (in this case, glucose) does not affect any covariates used as regressors and *2*) there is no confounding within levels of the other covariates. These assumptions may not be valid when the exposure and covariates vary over time, because a covariate may be affected by the exposure and also be a confounder. Such may be the case for blood pressure and serum cholesterol concentration in the present study. For example, high blood pressure may be a confounder because it is a known risk factor for early death and is found more frequently in patients with hyperglycemia. But blood pressure also rises as a consequence of hyperglycemia (10,11). High blood pressure may therefore be both a confounder and an intermediate variable on the causal pathway between glucose concentration and mortality, and a proportional-hazards analysis that includes blood pressure as a time-dependent covariate will underestimate the effect of glucose on mortality (42). Similarly, including serum cholesterol concentration in the model, as has been done frequently in the past (6–8,18,20,22), may also lead to a biased estimate of the effect of glucose on mortality. Nevertheless, exclusion of these variables may also result in a biased estimate. Accordingly, we examined the effect of glucose on mortality by using two models, but we favored the model that did not control for blood pressure or serum cholesterol concentration (Table 4) because each is undoubtedly an intermediate variable in the pathway of interest. The validity of this model will be reduced to the extent that these variables also confound the effect of interest. Inclusion of blood pressure and cholesterol in the analyses (Table 5) reduced the effect of plasma glucose concentration on deaths from cardiovascular disease but did not reduce the effect of glucose on deaths from diabetes-related diseases.

Fewer than 1% of adult Pima Indians smoke one pack or more of cigarettes per day (38,43). Thus, heavy smoking in this population is not a prominent risk factor for diabetic microvascular disease (43) or heart disease (38), and because of the low frequency, it was not included as a covariate in the present study. In addition, the effect of serum insulin concentration was not examined, because neither fasting nor 2-h postload insulin concentration predicted the development of electrocardiographic abnormalities in Pima Indians (44), which suggests that serum insulin does not have an important atherogenic role in this population.

In conclusion, higher baseline 2-h postload plasma glucose concentration strongly predicted deaths from cardiovascular and diabetic nephropathy in Pima Indians with type 2 diabetes. The response was nearly linear, which suggests a dose-response relationship similar to that reported in other populations (7,8,19–22). By contrast, higher glucose concentrations had almost no effect on other natural causes of death. Although lower as well as higher glucose concentrations predicted deaths from renal disease in the time-dependent analysis, this finding illustrates an important effect of uremia on insulin resistance and does not suggest that aggressive glycemic control should not be maintained. Such control is encouraged for most patients with type 2 diabetes because it substantially decreases the risk of microvascular disease and may have a modest beneficial effect on deaths from cardiovascular disease (45).

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REFERENCES

1. Kannel WB, McGee DL: Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham Study. *Diabetes Care* 2:120–126, 1979
2. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434–444, 1993
3. Borch-Johnsen K, Andersen PK, Deckert T: The effect of proteinuria on relative mortality in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 28:590–596, 1985
4. Nelson RG, Pettitt DJ, Carraher MJ, Baird HR, Knowler WC: Effect of proteinuria on mortality in NIDDM. *Diabetes* 37:1499–1504, 1988
5. Sievers ML, Nelson RG, Knowler WC, Bennett PH: Impact of NIDDM on mortality and causes of death in Pima Indians. *Diabetes Care* 15:1541–1549, 1992
6. West KM, Ahuja MMS, Bennett PH, Czyzyk A, De Acosta OM, Fuller JH, Grab B, Grabauskas V, Jarrett RJ, Kosaka K, Keen H, Krolewski AS, Miki E, Schliack V, Teuscher A, Watkins PH, Stober JA: The role of circulating glucose and triglyceride concentrations and their interactions with other "risk factors" as determinants of arterial disease in nine diabetic population samples from the WHO Multinational Study. *Diabetes Care* 6:361–369, 1983
7. Uusitupa MIJ, Niskanen LK, Siitonen O, Voutilainen E, Pyörälä K: Ten-year cardiovascular mortality in relation to risk factors and abnormalities in lipoprotein composition in type 2 (non-insulin-dependent) diabetic and non-diabetic subjects. *Diabetologia* 36:1175–1184, 1993
8. Lehto S, Rönnemaa T, Haffner SM, Pyörälä K, Kallio V, Laakso M: Dyslipidemia and hyperglycemia predict coronary heart disease events in middle-aged patients with NIDDM. *Diabetes* 46:1354–1359, 1997
9. Reaven GM: Banting Lecture 1988: Role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988
10. Jarrett RJ, Keen H, McCartney M, Fuller JH, Hamilton PJ, Reid DD, Rose G: Glucose tolerance and blood pressure in two population samples: their relationship to diabetes mellitus and hypertension. *Int J Epidemiol* 7:15–24, 1978
11. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Mott DM, Bennett PH: Insulin and hypertension: relationship to obesity and glucose intolerance in Pima Indians. *Diabetes* 39:1430–1435, 1990
12. Pyörälä K: Relationship of glucose tolerance and plasma insulin to the incidence of coronary heart disease: results from two population studies in Finland. *Diabetes Care* 2:131–141, 1972
13. Makita Z, Radoff S, Rayfield EJ, Yang Z, Skolnik E, Delaney V, Friedman EA, Cerami A, Vlassara H: Advanced glycosylation end products in patients with diabetic nephropathy. *N Engl J Med* 325:826–842, 1991
14. Colwell JA: Vascular thrombosis in type II diabetes (Editorial). *Diabetes* 42:8–11, 1993
15. Steinberg D, Parthasarathy S, Carew TE, Khou JC, Witztum JL: Beyond cholesterol: modifications of low-density lipoprotein that increase its atherogenicity. *N Engl J Med* 320:915–924, 1989
16. Nelson RG, Knowler WC, Pettitt DJ, Hanson RL, Bennett PH: Incidence and determinants of elevated urinary albumin excretion in Pima Indians with NIDDM. *Diabetes Care* 18:182–187, 1995
17. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
18. Singer DE, Nathan DM, Anderson KM, Wilson PWF, Evans JC: Association of HbA_{1c} with prevalent cardiovascular disease in the original cohort of the Framingham Heart Study. *Diabetes* 41:202–208, 1992
19. Andersson DKG, Svärdsudd K: Long-term glycemic control relates to mortality in type II diabetes. *Diabetes Care* 18:1534–1543, 1995
20. Kuusisto J, Mykkänen L, Pyörälä K, Laakso M: NIDDM and its metabolic control predict coronary heart disease in elderly subjects. *Diabetes* 43:960–967, 1994
21. Klein R: Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care* 18:258–268, 1995
22. Wei M, Gaskill SP, Haffner SM, Stern MP: Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality: the San Antonio Heart Study. *Diabetes Care* 21:1167–1172, 1998
23. Burke JP, Haffner SM, Stern MP: Effect of glucose level on non-cardiovascular disease mortality in patients with type 2 diabetes (Abstract). *Diabetes* 47(Suppl. 1):A148, 1998
24. Bennett PH, Burch TA, Miller M: Diabetes mellitus in American (Pima) Indians. *Lancet* ii:125–128, 1971
25. Sievers ML, Nelson RG, Bennett PH: Sequential trends in overall and cause-specific mortality in diabetic and nondiabetic Pima Indians. *Diabetes Care* 19:107–111, 1996
26. World Health Organization: *Diabetes Mellitus*. Geneva, World Health Org., 1985 (Tech. Rep. Ser. no. 727)
27. Sievers ML, Nelson RG, Bennett PH: Adverse mortality experience of a southwestern American Indian Community: overall death rates and underlying causes of death in Pima Indians. *J Clin Epidemiol* 43:1231–1242, 1990
28. Data Preparation Branch: *Vital Statistics Instruction Manual Part 2a. Instructions for Classifying the Underlying Cause of Death, 1986*. Hyattsville, MD, U.S. Department of Health and Human Services, Public Health Service, National Center for Health Statistics, 1985
29. Data Preparation Branch: *Vital Statistics Instruction Manual Part 2b. Instructions for Classifying Multiple Causes of Death, 1986*. Hyattsville, MD, U.S. Department of Health and Human Services, Public Health Service, National Center for Health Statistics, 1985
30. Data Preparation Branch: *Vital Statistics Instruction Manual Part 2c. ICD-9 ACNE Decision Tables for Classifying Underlying Causes of Death, 1986*. Hyattsville, MD, U.S. Department of Health and Human Services, Public Health Service, National Center for Health Statistics, 1985
31. Data Preparation Branch: *Vital Statistics Instruction Manual Part 4. Demographic Classification and Coding Instructions for Death Records, 1986*. Hyattsville, MD, U.S. Department of Health and Human Services, Public

Health Service, National Center for Health Statistics, 1985
32. U.S. Department of Health and Human Services, Public Health Service: *Physicians' Handbook on Medical Certification: Death, Birth, Fetal Death.* Hyattsville, MD, U.S. Department of Health and Human Services, Public Health Service, National Center for Health Statistics, 1978, p. 1–30 (DHHS publ. no. [PHS] 81–1108)
33. U.S. National Center for Health Statistics: *The International Classification of Disease, 9th Revision, Clinical Modification,* Vol. 1. Ann Arbor, MI, Edwards Brothers, 1978
34. Hastie T, Tibshirani R: *Generalized Additive Models.* London, Chapman and Hall, 1990
35. Hastie T, Tibshirani R: Generalized additive models for medical research. *Stat Methods Med Res* 4:187–196, 1995
36. Greenland S: Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. *Epidemiology* 6:356–365, 1995
37. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A: Albuminuria reflects widespread vascular damage: the Steno Hypothesis. *Diabetologia* 32:219–226, 1989
38. Nelson RG, Sievers ML, Knowler WC, Swinburn BA, Pettitt DJ, Saad MF, Liebow IM, Howard BV, Bennett PH: Low incidence of fatal coronary heart disease in Pima Indians despite high prevalence of non-insulin-dependent diabetes. *Circulation* 81:987–995, 1990
39. Nelson RG, Hanson RL, Pettitt DJ, Knowler WC, Bennett PH: Survival during renal replacement therapy for diabetic end-stage renal disease in Pima Indians. *Diabetes Care* 19:1333–1337, 1996
40. Sievers ML, Nelson RG, Bennett PH: Decrease in mortality from diabetic nephropathy in Pima Indians (Letter). *Diabetes Care* 19:777, 1996
41. UK Prospective Study Group: UK Prospective Diabetes Study (UKPDS). VIII. Study design, progress and performance. *Diabetologia* 34:877–890, 1991
42. Kalbfleisch JD, Prentice RL: *The Statistical Analysis of Failure Time Data.* Wiley, New York, 1980
43. Nelson RG, Wolfe JA, Horton MB, Pettitt DJ, Bennett PH, Knowler WC: Proliferative retinopathy in NIDDM: incidence and risk factors in Pima Indians. *Diabetes* 38:435–440, 1989
44. Liu QZ, Knowler WC, Nelson RG, Saad MF, Charles MA, Liebow IM, Bennett PH, Pettitt DJ: Insulin treatment but not endogenous insulin concentration is associated with ECG abnormalities in diabetic Pima Indians. *Diabetes* 41:1141–1150, 1992
45. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998