Effects of Diabetes and Level of Glycemia on All-Cause and Cardiovascular Mortality

The San Antonio Heart Study

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OBJECTIVE — Although the level of hyperglycemia is clearly a risk factor for microvascular complications in diabetic patients, its role in macrovascular complications remains controversial. We followed 4,875 subjects (65% Mexican-American) for 7–8 years to investigate the effects of diabetes and hyperglycemia on all-cause and cardiovascular disease (CVD) mortality. These end points were also analyzed according to quartiles of baseline fasting plasma glucose among diabetic participants.

RESEARCH DESIGN AND METHODS — The Cox proportional hazards model was used to estimate the relative risks (RRs) for all-cause and CVD mortality.

RESULTS — Diabetes was significantly associated with increased all-cause mortality (RR [95% CI] = 2.1 [1.3–3.5] in men; 3.2 [1.9–5.4] in women) and increased CVD mortality (3.2 [1.4–7.1] in men; 8.5 [2.8–25.2] in women). Among diabetic subjects, those in quartile 4 had a 4.2-fold greater risk of all-cause mortality ($P < 0.001$) and a 4.7-fold greater risk of CVD mortality ($P = 0.01$) than those in quartiles 1 and 2 combined. After further adjustment for other potential risk factors, subjects in quartile 4 had a 4.9-fold greater risk of all-cause mortality and a 4.9-fold greater risk of CVD mortality than those in quartiles 1 and 2. In addition, hypertension, current smoking, and cholesterol >6.2 mmol/l were significant predictors of CVD mortality using Cox models.

CONCLUSIONS — We conclude that diabetes is a predictor of both all-cause and CVD mortality in the general population and that both hyperglycemia and common CVD risk factors are important predictors of all-cause and CVD mortality in diabetic subjects.

Several clinical and epidemiological studies have demonstrated that type 2 diabetic subjects have higher cardiovascular disease (CVD) mortality than the general population (1–3). An unfavorable cardiovascular risk factor profile may be an explanation. However, even after controlling for risk factors such as current smoking, hypertension, or high cholesterol, CVD death rates are higher in diabetic subjects than in nondiabetic subjects. High fasting plasma glucose has been suspected to play an important role in increased CVD among diabetic subjects. However, early cross-sectional studies did not support this hypothesis (4). Recently, several prospective studies have demonstrated that abnormalities in glucose metabolism are associated with increased CVD and all-cause mortality in diabetic subjects (5–8). Moreover, in the East-West Finland Study, involving >1,000 diabetic subjects followed for 7 years, the effects of glycemia on both fatal and nonfatal coronary heart disease (CHD) end points were independent of other cardiovascular risk factors, notably lipids and lipoproteins, which were themselves significant predictors of CHD end points (6). These issues, however, have not been addressed in Mexican-Americans. We have previously reported that Mexican-Americans have a high prevalence and incidence of diabetes (9,10). In addition, a previous analysis showed that diabetes was associated with high CVD and all-cause mortality in this population (3). However, a sex-specific analysis was not performed at that time because of the small sample size resulting from partial follow-up of the overall cohort. We have now completed the follow-up on the entire cohort and have, therefore, reanalyzed the association between diabetes and all-cause and CVD mortality by sex. In addition, we have assessed the effects of risk factors on all-cause and CVD mortality in diabetic participants.

RESEARCH DESIGN AND METHODS

— Details of the study design and sampling, recruitment, and field procedures of the San Antonio Heart Study have been reported previously (9–13). Briefly, participants were recruited into the San Antonio Heart Study in two phases. The first phase extended from October 1979 to November 1982 and the second phase from October 1984 to October 1988. Households were randomly sampled from three types of neighborhoods: low-income barrios, middle-income transitional neighborhoods, and high-income suburbs. All men and nonpregnant women between 25 and 64 years of age residing in the selected households were considered eligible for the study and were invited to undergo a physical examination in a mobile clinic. Blood specimens were obtained after a 12-h fast, and all lipid and lipoprotein measurements were made in the fasting state. A single glucose tolerance test was performed on each subject. The combined response rate for both phases of the study was 65.3%. The

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Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; ICD-9, *International Classification of Diseases, Ninth Revision*; RR, relative risk; WHO, World Health Organization.

Table 1—*Baseline characteristics of participants in the San Antonio Heart Study*

	Women		Men	
	Type 2 diabetic subjects	Nondiabetic subjects	Type 2 diabetic subjects	Nondiabetic subjects
n	281	2,494	190	1,910
Age (years)	52.5 ± 9.0	42.8 ± 11.0†	52.9 ± 8.5	42.7 ± 11.3
Mexican-Americans (%)	82.0	62.9†	78.4	60.6%†
BMI (kg/m^2)	32.0	26.8†	29.9	27.4 ± 4.3†
Total cholesterol (mmol/l)	5.60 ± 1.24	5.15 ± 1.10†	5.50 ± 1.36	5.30 ± 1.03*
HDL cholesterol (mmol/l)	1.16 ± 0.34	1.35 ± 0.30†	1.03 ± 0.36	1.12 ± 0.30†
Triglyceride (mg/dl)	193.7 ± 103.5	121.5 ± 91.0†	228.9 ± 164.6	160.3 ± 113†
Diastolic blood pressure (mmHg)	73.7 ± 9.4	69.8 ± 8.9†	76.3 ± 9.7	74.1†
Systolic blood pressure (mmHg)	126.1 ± 16.5	112.3 ± 15.1†	128.7 ± 16.5	119.3 ± 13.5†
Fasting glucose (mmol/l)	9.07 ± 3.72	4.78 ± 0.62†	8.90 ± 3.17	4.95 ± 0.58†
2-h glucose (mmol/l)	16.73 ± 5.49	6.06 ± 1.76†	16.4 ± 4.64	5.66 ± 1.79†
Fasting insulin (pmol/l)	168.0 ± 227.4	76.8 ± 99.6†	150.6 ± 208.2	83.4 ± 87.6†
Education level (years)	8.3 ± 4.6	11.5 ± 3.9†	10.5 ± 4.3	12.7 ± 4.0†
Alcohol user (%)	3.2	3.0	20.0	20.7
Exercise ≥1/week (%)	21	44†	33.7	46.4†
Current smoking (%)	25	23	35.8	33.7
History of:				
Heart attack (%)	3.5	1.2*	12.1	3.5†
Angina pectoris (%)	7.7	4.9	5.8	2.5
Cancer (%)	1.4	0.8	3.1	0.7

Data are *n*, means ± SD, or %. *$P < 0.05$, †$P < 0.005$ for difference between diabetic and nondiabetic participants.

study was approved by the University of Texas Health Science Center Institutional Review Board, and all participants gave informed consent.

Diabetes was defined according to the plasma glucose criteria of the World Health Organization (WHO) (14): fasting plasma glucose level ≥7.8 mmol/l or 2-h postload glucose level ≥11.1 mmol/l. Participants who did not meet these criteria but who gave a history of diabetes and reported current therapy with either oral antidiabetic agents or insulin were also considered to have diabetes. A total of 471 subjects (380 Mexican-Americans and 91 non-Hispanic whites) were classified as having diabetes at baseline. Of these, 231 were newly diagnosed at the time of their survey examination. Of the 240 who had been previously diagnosed, 62 were on insulin, 106 were on oral agents, and the remainder were on diet treatment only.

In October 1987, a follow-up study was initiated to determine the incidence of diabetes and CVD, as well as mortality rates. An 8-year follow-up has been completed on the participants enrolled in phase I, and a 7-year follow-up has been completed on the phase II participants. Detailed descriptions of the follow-up survey have been published previously (10,12). Vital status was ascertained for 98.1% of the total cohort and 99% of those with type 2 diabetes at baseline. Deaths were identified and confirmed by follow-up interviews with next-of-kin, after which death certificates were obtained. The death certificates were then sent to the Medical Coding and Consultation Services (Rolesville, NC) for coding according to the *International Classification of Diseases, Ninth Revision* (ICD-9) by a certified nosologist. Cause of death was defined as the underlying cause of death. The ICD-9 codes used for CVD were 390–459. Individuals whose vital status was unknown at the time of the follow-up survey and those with type 1 diabetes or whose baseline plasma glucose concentrations were unknown are excluded from the present analyses. Although analyses were carried out in the overall sample to compare diabetic with nondiabetic participants, the major emphasis in this study is on risk factors in participants with type 2 diabetes.

Hypertension was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg. Participants who reported a history of hypertension and use of antihypertensive medications were also considered to have hypertension. Serum cholesterol concentrations were categorized as high (>6.2 mmol/l), intermediate (4.1–6.2 mmol/l), or low (<4.1 mmol/l).

Death rates were calculated by dividing the number of deaths occurring during the study period by the number of person-years of observation. The period of observation was defined as the interval between the baseline and follow-up visits or, in the case of deceased individuals, the interval between their baseline visit and the date of death. Age-adjusted death rates were calculated by the SAS program and expressed per 1,000 person-years of observation. The Cox proportional hazards model was used to estimate the relative risks (RRs) of mortality, adjusting for covariates (15). Only baseline measurements were used to predict mortality, since no intermediate risk factor measurements were made before the 7–8-year follow-up examination that represented the close-out date for the present mortality follow-up. Both full and restricted models were considered. A ≥10% change in the magnitude of a main effect was used as the criterion to decide whether a potential confounding variable remained in the restricted model (16,17). To evaluate the possibility of sex differences in the relationship between risk factors and mortality, interaction terms between sex and other independent variables were entered into the initial models. However, no significant interactions were found. All *P* values were calculated using two-tailed tests.

Table 2—*Age- and ethnicity-adjusted all-cause and CVD mortality per 1,000 person-years according to quartiles of baseline fasting plasma glucose concentration among participants with type 2 diabetes*

	Quartiles 1 and 2	Quartile 3	Quartile 4
n	236	119	116
Fasting glucose (mmol/l)	<8.0	8.0–11.5	>11.5
All-cause mortality			
Men	8.8	23.1	28.2
Women	6.2	11.1	24.8
All*	7.2	16.4	26.4
CVD mortality			
Men	4.4	9.3	10.6
Women	1.7	3.9	12.2
All*	2.8	6.3	11.6

*Adjusted for age, sex, and ethnic group; $P < 0.05$ in tests for trend.

RESULTS — The baseline characteristics of the 4,875 study participants by sex and diabetes status are shown in Table 1. Compared with participants without diabetes, participants with type 2 diabetes were older, were more often Mexican-American, and had higher BMI, total cholesterol, triglyceride, diastolic blood pressure, systolic blood pressure, fasting insulin, and self-report of physician-diagnosed heart attack, but lower levels of HDL cholesterol, less leisure time physical activity, and lower educational attainment.

After an average of 7.5 years of follow-up, 162 deaths, including 51 CVD deaths, occurred. For both men and women, those with type 2 diabetes had higher CVD and all-cause mortality than those without diabetes. For CVD mortality, the age- and ethnicity-adjusted RR due to diabetes was 3.2 (95% CI 1.4–7.1) for men and 8.5 (2.8–25.2) for women. For all-cause mortality, age- and ethnicity-adjusted RR was 2.1 (1.3–3.5) for men and 3.2 (1.9–5.4) for women. These RRs were changed little after adjustment for cardiovascular risk factors such as cigarette smoking, hypertension, and high cholesterol.

Among type 2 diabetic subjects, there were 49 all-cause deaths, including 20 CVD deaths. As shown in Table 2, the age-, sex-, and ethnicity-adjusted all-cause death rate per 1,000 person-years was 26.4 for those with fasting plasma glucose >11.5 mmol/l (quartile 4), 16.4 for those with fasting plasma glucose between 8.0 and 11.5 mmol/l (quartile 3), and 7.2 for those with fasting plasma glucose <8.0 mmol/l (quartiles 1 and 2 combined). (Quartiles 1 and 2 were combined because of the low number of deaths in quartile 1.) These trends appeared in both men and women. The CVD death rate per 1,000 person-years was 11.6 for quartile 4, 6.3 for quartile 3, and 2.8 for quartiles 1 and 2 combined. Similar trends appeared in both men and women. Interestingly, the male excess in both all-cause and CVD mortality disappeared in the highest quartile of fasting plasma glucose, although it was strongly evident in the lower quartiles.

Table 3 shows that apart from glucose itself, four variables showed statistically significant differences across glucose quartiles. Duration of diabetes and triglyceride levels were positively associated, and HDL cholesterol was inversely associated, with the levels of fasting plasma glucose. There were also more Mexican-Americans than non-Hispanic whites in the higher glucose quartiles.

Tables 4 and 5 show Cox proportional hazards models of the effects of risk factors on all-cause and CVD mortality in diabetic participants. All models are adjusted for age, sex, and ethnicity. For the models on the left side of the tables, each of the other risk factors is examined one at a time, and for the models on the right side of the tables, all risk factors are entered into the models simultaneously. The initial models contained, in addition to the risk factors shown in the tables, BMI, triglyceride, HDL cholesterol, diabetes duration, educational level, physical activity, and angina, but because these variables did not meet the criterion for entry into the models (see METHODS), they are not included in the final models presented in the tables.

Table 3—*Baseline characteristics according to quartiles of baseline fasting plasma glucose concentration among type 2 diabetic subjects*

	Quartiles 1 and 2	Quartile 3	Quartile 4
n	236	119	116
Age (years)	52.9 ± 0.6	52.4 ± 0.8	51.9 ± 0.8
Sex (% male)	41	45	36
Mexican-Americans (%)	73	84*	89†
BMI (kg/m^2)	30.6	31.8	31.5
Total cholesterol (mmol/l)	5.46 ± 0.09	5.66 ± 0.12	5.77 ± 0.12
HDL cholesterol (mmol/l)	1.15 ± 0.02	1.09 ± 0.03	1.04 ± 0.03†
Triglyceride (mg/dl)	181 ± 9.1	233 ± 12.4*	245 ± 12.6†
Diastolic blood pressure (mmHg)	74.9 ± 0.6	75.2 ± 0.8	73.4 ± 0.9
Systolic blood pressure (mmHg)	128 ± 1.1	127 ± 1.4	124 ± 1.5
Fasting glucose (mmol/l)	6.28 ± 0.09	9.56 ± 0.12*	14.39 ± 0.12†
2-h glucose (mmol/l)	13.56 ± 0.23	17.67 ± 0.28*	23.28 ± 0.34†
Fasting insulin (pmol/l)	144.0 ± 15.0	186.0 ± 22.2	169.8 ± 22.8
Duration of diabetes (years)	2.7 ± 0.5	5.9 ± 0.6*	6.4 ± 0.6†
Education level (years)	9.4 ± 0.3	9.2 ± 0.4	8.4 ± 0.4
Alcohol use (%)	13	6.2	6.4
Exercise ≥1 week (%)	27	26	28
Current smoking (%)	29	29	31
History of:			
Heart attack (%)	8.8	6.2	4.8
Angina pectoris (%)	5.5	8.5	8.8
Cancer (%)	1.3	3.9	2.4

Data are *n*, means ± SD, or %. *$P < 0.05$ for quartile 3 compared with quartiles 1 and 2 combined; †$P < 0.05$ for quartile 4 compared with quartiles 1 and 2 combined.

Table 4—*Adjusted RRs (and 95% CIs) for all-cause mortality for selected risk factors among participants with type 2 diabetes*

	n	Ethnicity, age, and sex adjustment	Multivariable adjustment
Glucose level			
Quartile 4	116	4.2 (2.0–8.8)	4.9 (2.3–10.3)
Quartile 3	119	2.8 (1.3–6.0)	2.8 (1.3–5.9)
Quartiles 1 and 2	236	1.0 (—)	1.0 (—)
Current smoking		1.8 (1.0–3.2)	1.7 (0.9–3.1)
Hypertension		1.5 (0.8–2.8)	2.3 (1.2–4.4)
High cholesterol		1.7 (1.0–3.0)	1.8 (1.0–3.2)
Heart attack		1.5 (0.6–3.7)	1.6 (0.7–3.9)
Cancer		19.4 (9.4–41.4)	19.1 (9.2–41.9)

Plasma glucose had a significant dose-response effect on all-cause mortality (Table 4). This effect is, if anything, enhanced by multivariable adjustment. Current smoking, high cholesterol, and cancer at baseline were significant predictors of all-cause mortality after adjusting for age, sex, and ethnicity, and the latter two associations remained statistically significant after multivariable adjustment. Hypertension and heart attack were also positively associated with all-cause mortality and, in the case of hypertension, this effect became statistically significant after multivariable adjustment. Fasting plasma insulin concentration was not a predictor of all-cause mortality in diabetic participants.

Table 5 shows a dose-response effect between glucose quartile and CVD mortality when adjusted for age, sex, and ethnicity; the effect in quartile 4 remained statistically significant after multivariable adjustment. The other risk factors also have positive associations with CVD mortality, all of which are statistically significant after multivariable adjustment.

CONCLUSIONS — The present findings confirm that diabetes is a strong and independent risk factor for both all-cause and, in particular, for CVD mortality. A number of studies have suggested that diabetes increases CVD risk more in women than in men, although this has not been a universal finding (1). Our study suggests that this effect occurs primarily in those diabetic individuals with the highest levels of glycemia. Specifically, we found that the sex difference in all-cause and CVD mortality among diabetic participants was quite evident in those with mild or moderate glycemia, but was nearly eliminated for those in the highest quartile of glycemia. This interaction of the sex difference with level of glycemia may account for some of the variable results reported in the literature (1). In the past, the role of glycemia as a cardiovascular risk factor was considered controversial, and many felt that it was a weak risk factor at best. This opinion probably derived, at least in part, from the negative results of the WHO Multinational Study (4). However, those results were cross-sectional. There was also a tendency to blur the distinction between glycemia as a risk factor in the general population as opposed to glycemia as a risk factor specifically among diabetic subjects (18). More recently, prospective data specifically on diabetic subjects have consistently shown glycemia to be a cardiovascular risk factor. However, these new data derive almost exclusively from Caucasian populations (5–8). Our study adds to this growing body of literature by indicating that the level of glycemia contributes independently to the excess in both all-cause and CVD mortality among individuals with type 2 diabetes and extends these findings to Mexican-Americans. It also confirms that this phenomenon can be demonstrated as readily with plasma glucose levels as with glycosylated hemoglobin. Also, as in the East-West Finnish Study (6), our results confirm that the effects of glycemia are independent of other conventional cardiovascular risk factors.

A dose-response relationship between level of hyperglycemia and both CVD deaths and all-cause mortality was observed. These associations held true even after adjustment for age, sex, total and HDL cholesterol, triglyceride, BMI, hypertension, cigarette smoking, and other potential confounders. Since a majority of our Mexican-American diabetic participants had low incomes and presumably had less access to health care, their fasting plasma glucose levels might represent their true (i.e., uncontrolled) long-term glycemic status.

There are several potential mechanisms that might explain why poor glycemic control of diabetes increases all-cause and CVD mortality. Hyperglycemia is associated with various other cardiovascular risk factors. Although our results indicate that the effect of hyperglycemia on mortality is independent of the risk factors that we measured, we cannot exclude the possibility that its effect is mediated by risk factors that we did not measure, such as small dense-LDL, plasminogen activator inhibitor-1, and perhaps others.

Hyperglycemia could also have a direct effect on vascular disease. It is associated with glycation of various tissue proteins and induces excessive cross-linking of collagen and other extracellular matrix proteins in vascular walls (19–22). It also stimulates the proliferation of smooth muscle cells and causes abnormalities in endothelial cell function leading to accelerated atherogenesis (19–22). In addition,

Table 5—*Adjusted RRs (and 95% CIs) for CVD mortality for selected risk factors among participants with type 2 diabetes*

	n	Ethnicity, age, and sex adjustment	Multivariable adjustment
Glucose level			
Quartile 4	116	4.7 (1.5–14.7)	4.9 (1.6–15.1)
Quartile 3	119	2.8 (0.8–9.3)	2.9 (0.9–9.8)
Quartiles 1 and 2	236	1.0 (—)	1.0 (—)
Current smoking		2.5 (1.0–6.1)	2.6 (1.1–6.5)
Hypertension		2.2 (0.9–5.6)	3.2 (1.2–8.4)
High cholesterol		2.7 (1.1–6.6)	2.5 (1.0–6.3)
Heart attack		3.0 (0.9–9.5)	4.3 (1.3–13.9)

hyperglycemia impairs the binding of apolipoprotein B-100 to LDL receptor. Glycated LDL has a prolonged half-life and is therefore susceptible to increased oxidation. It is believed that oxidized LDL is more atherogenic than native LDL (23).

Even though hyperglycemia was found to be predictive of CVD mortality, it is important to distinguish between the effects of insulin and the effects of hyperglycemia itself. The potential atherogenic role of insulin has been controversial. A number of animal studies have supported an atherogenic effect of insulin (24). However, of six prospective human studies, three failed to demonstrate an association between insulinemia and CVD (25). Two recent studies, however, which used specific insulin assays that do not cross-react with proinsulin or other insulin precursors, reported positive associations between fasting insulin and CVD among nondiabetic individuals (26,27). In addition, the Atherosclerosis Risk in Communities (ARIC) Study found a positive association in women, but not in men (28). This is a distinction from all previous positive studies on this topic, which showed associations only in men. In our 7.5-year follow-up study, 20% of participants with fasting insulin >202 pmol/l had asymptomatic diabetes, and another 27% developed diabetes during follow-up. Therefore, the effects of diabetes on CVD may account for part of the reported association between insulinemia and CVD. However, irrespective of the role that insulin plays in the development of CVD, the association between fasting insulinemia and level of hyperglycemia was nonlinear in our data (Table 3). Thus, the association we observed between hyperglycemia and CVD and all-cause mortality in diabetic subjects was not confounded by fasting insulin levels.

Our results are consistent with, although they do not prove, the concept that improved glycemic control might reduce cardiovascular risk in patients with diabetes. Only a clinical trial can provide definitive evidence on this important clinical topic. In addition, a conclusive demonstration that glycemic lowering could favorably alter cardiovascular risk in diabetic subjects would in no way negate the importance of treating other conventional cardiovascular risk factors in these patients. Even if endogenous hyperinsulinemia is atherogenic in nondiabetic individuals, our failure to find insulin to be a predictor of mortality among diabetic individuals is reassuring and suggests that aggressive glycemic control with exogenous insulin is not harmful to diabetic patients. Again, only a suitable clinical trial can definitely resolve this issue. Lastly, further research on the mechanisms whereby glycemia might enhance atherogenesis is needed.

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