Sex Differences in the Impact of Coexistent Diabetes on Survival in Patients With Coronary Heart Disease

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OBJECTIVE — To evaluate the sex difference in the impact of diabetes on survival in patients with coronary heart disease.

RESEARCH DESIGN AND METHODS — Cohort study based on a sample from a hospital registry in Chicago, IL. A total of 974 consecutive patients (585 men and 389 women) with angiographically confirmed coronary artery disease were followed for 4.6 yr.

RESULTS — At baseline, 160 men and 155 women had diabetes. The age-adjusted relative risk of death from all causes for patients with diabetes versus patients without diabetes was 0.93 (95% confidence interval 0.65–1.34) in men and 1.99 (95% CI 1.30–3.05) in women. For cardiac death, the corresponding relative risk was 1.00 (95% CI 0.64–1.56) and 1.96 (95% CI 1.19–3.24) in men and women, respectively. Baseline differences in age, hypertension, body mass index, number of diseased vessels, and ejection fraction did not fully explain the excess mortality risk in diabetic women. Excess risk was apparent in both cardiac and noncardiovascular categories. Among nondiabetic patients, the risk of death was significantly lower in women compared with men (multivariate-adjusted relative risk = 0.61, 95% CI 0.41–0.89). However, the mortality risk of diabetic women became similar to men as a whole (relative risk = 1.13, 95% CI 0.80–1.60).

CONCLUSIONS — Diabetes confers a substantially higher risk of mortality in women than in men when it occurs in the presence of coronary heart disease.

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CHD, CORONARY HEART HISEASE: CI, CONFIDENCE INTERVAL; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; MI, MYOCARDIAL INFARCTION; EF, EJECTION FRACTION; NON-CVD, NONCARDIOVASCULAR DISEASE; BMI, BODY MASS INDEX; RR, RELATIVE RISK; HDL, HIGH-DENSITY LIPOPROTEIN; NHANES, NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY.

At all ages, women in the U.S. experience lower mortality than men. In the presence of certain disease states, however, relative survival differences between men and women may either disappear or reverse; two of these conditions are CHD (1–2) and diabetes (3–6). Little is known about sex-related differences in the impact of diabetes on mortality in patients with angiographically-defined coronary atherosclerosis. This study examines the impact of diabetes on survival in men and women with confirmed CHD in a hospital-based heart disease registry.

RESEARCH DESIGN AND METHODS

— Cook County Hospital is a 650 bed, public general hospital in Chicago, IL serving a primarily minority, low-income population. Between January 1983 and March 1989, 2315 consecutive patients were enrolled in the Cook County Heart Disease Registry. All consecutive patients who had cardiac catheterization for the diagnostic evaluation of presumed CHD, or were hospitalized for acute MI, or underwent coronary artery bypass grafting were eligible for the registry. Among these patients, 1992 patients had angiography. Significant CHD was found in 1008 (50.6%) patients. Information about diabetes was missing in 34 patients, and they were excluded from this analysis. The final cohort selected for this study thus consisted of a total of 974 patients (585 men and 389 women) with confirmed CHD.

Patients were interviewed by the on-service medical resident and later by the cardiovascular fellow through use of a standardized questionnaire before catheterization. Coronary cineangiograms were obtained in multiple projections, including angulated views in the sagittal plane. Left ventricular angiograms were obtained in the standard 30°C right anterior oblique projection, and the EF was calculated with the single plane method of Dodge. Significant CHD was defined as a ≥70% reduction in the cross-

sectional area and categorized as involving one to three major vessels. Left main stenosis with a ≥50% narrowing was assigned three-vessel disease for the overall analysis, and low EF was defined as <45%. Patients who reported a diagnosis of diabetes, or who currently were taking insulin or oral hypoglycemic agents, were defined as diabetic cases. Based on their clinical and demographic characteristics, we assumed these patients had primarily NIDDM. No information on the duration of diabetes was obtained.

An attempt was made to contact all patients either during an outpatient visit, by telephone, or by review of medical records of clinic attendance. In addition, the database provided by the National Death Index, which contains a standard set of identifying data for each decedent of the nation, was searched annually until 31 December 1990 for all members of the original cohort (7). Death certificates of the decedents were obtained from the department of public health in the states where the patients died. Causes of death were coded independently through a review of the death certificates by either of two physicians (Y.L. or J.K.G) and classified into 22 disease categories. For these analyses, causes of death were further grouped into the following categories: acute MI, CHD, cardiac diseases, infection, renal failure, and non-CVDs. We recognize a possible tendency to record CHD as the underlying cause of death on the death certificates for patients with a prior diagnosis of CHD. Also, patients with diabetes often died from multiple complications. The multiple cause-of-death approach, instead of coding for only the underlying cause, was used.

Statistical analysis

Comparisons of baseline characteristics between diabetic and nondiabetic patients were made for men and women separately by using the χ^2 test and a two-tailed Student's t test where appropriate. Cumulative survival rates were calculated by the life table method. Survival curves of diabetic and nondiabetic patients were compared by using the log-rank test. Cox's proportional hazard model was used to examine the risk of death for diabetic versus nondiabetic patients adjusting for baseline differences in age, race, BMI, medical history of MI, hypertension, number of diseased vessels, and EF. RRs and 95% CIs were derived from Cox's regression coefficients.

Additional analyses were made after exclusion of patients hospitalized for acute MI before or after the angiogram (n = 192) and with the criterion of a ≥50% diameter reduction of the vessel as significant CHD (n = 1121). Similar results were obtained and are not presented in this study. Analyses were performed separately for all races, blacks only (n = 686, 70%), and nonblacks only (n = 288, 30%), which included whites (n = 96), Hispanics (n = 80), Indians or Pakistanis (n = 69), and others (n = 43).

RESULTS — The baseline characteristics for diabetic and nondiabetic men and women patients are presented in Table 1. For both men and women, diabetic patients were significantly older and had higher rates of hypertension. BMI was significantly higher for diabetic versus nondiabetic women. Compared with nondiabetic women, diabetic women had a lower mean EF and a higher percentage of EFs <45%; these differences were borderline significant (P = 0.06 and 0.08, respectively). Diabetic patients had more three-vessel disease and less one-vessel disease than did nondiabetic patients among both men and women; statistical significance was achieved only in women. Women as a whole had less severe coronary artery obstruction than did men. However, the severity of CHD in diabetic women was greater than the average for all men combined and similar to diabetic men. During a mean follow-up of 4.6 yr (range 0–8), 237 patients died. Survival curves for patients with and without diabetes by sex are presented in Fig. 1. Although nondiabetic men had slightly more favorable survival experience than did diabetic men, the difference was not statistically significant. With cardiac death as the end point, the life-table 4-yr cumulative mortality rates were similar between diabetic and nondiabetic men (12 vs. 15%, P = 0.985) and twice as high in diabetic women compared with nondiabetic women (19 vs. 9%, P = 0.004) (data not shown). Distribution of various causes of death are listed in Table 2. Men with diabetes had similar mortality rates from cardiac diseases, CHD, acute MI, or non-CVD as men without diabetes. They were, on the other hand, more likely to die from infection and renal failure; the total number of these events was small, however. Diabetic women, compared with nondiabetic women, had fourfold the rates of death from acute MI and renal failure and twofold for cardiac diseases, CHD, and non-CVDs. The increase in risk of death associated with diabetes in women was similar for both cardiac and non-CVDs.

RRs and 95% CIs for death from all causes and cardiac diseases between pairs of the 4 subgroups (i.e., diabetes and nondiabetes, men and women) are provided in Table 3. No excess risk of either fatal end points was found for diabetic compared with nondiabetic men, after adjustment for age and other baseline variables. The age-adjusted risk of death was almost 100% higher in diabetic compared with nondiabetic women. With adjustment for race, BMI, medical history of MI, and hypertension, the RR of death from all causes and cardiac diseases with diabetes was 2.07 (95% CI 1.34–3.20) and 2.08 (95% CI 1.24–3.47), repectively. After additional adjustment for the number of diseased vessels and EF, the RRs decreased to 1.80 for both fatal end points (Table 3). This finding suggests that more severe vessel involvement and reduced left ventricular systolic function explain 25% of the ef-

Table 1— *Baseline characteristics of patients with angiographically confirmed CHD by sex and diabetic status*

	MEN			WOMEN		
	DIABETIC	NONDIABETIC	TOTAL	DIABETIC	NONDIABETIC	TOTAL
n	160	425	585	155	234	389
AGE (YR)	57.3 ± 8.5*	55.1 ± 9.1	55.7 ± 9.0	59.1 ± 7.2†	57.2 ± 8.8	58.0 ± 8.2
RACE (% BLACKS)	68.1	60.7	62.7	82.9	80.6	82.0
BMI (KG/M^2)	27.9 ± 4.9	27.2 ± 4.6	27.4 ± 4.7	30.2 ± 6.2†	28.8 ± 5.8	29.4 ± 6.0
MEDICAL HISTORY						
PRIOR MI (%)	40.0	47.1	45.1	30.3	30.3	30.3
HYPERTENSION (%)	73.8†	64.5	67.0	81.9†	71.8	75.8
STROKE (%)	3.1	4.0	3.8	3.9	2.1	2.8
USE OF INSULIN (%)	50.7	—	—	53.3	—	—
ANGIOGRAPHIC FINDINGS						
MEAN PULMONARY ARTERY PRESSURE (MMHG)	19.7 ± 8.1	20.3 ± 9.1	20.1 ± 8.8	21.1 ± 8.7	19.6 ± 8.1	20.2 ± 8.4
MEAN AORTIC PRESSURE (MMHG)	101 ± 16	101 ± 16	101 ± 16	103 ± 18	104 ± 17	103 ± 17
LEFT VENTRICULAR END DIASTOLIC PRESSURE (MMHG)	14.3 ± 6.9	14.0 ± 6.5	14.1 ± 6.6	13.4 ± 6.5	13.6 ± 7.1	13.5 ± 6.8
EF (%)	56 ± 15	58 ± 15	57 ± 15	61 ± 16	64 ± 15	63 ± 15
LOW EF (%)	24.8	22.4	23.1	16.1	10.1	12.5
DISEASED VESSELS (*n*)						
ONE (%)	29.4	33.4	32.3	29.0	41.9	36.8
TWO (%)	26.3	27.8	27.4	26.5 †	26.5	26.5
THREE (%)	44.4	38.8	40.3	44.5	31.6	36.8

Data for continuous variables are means ± SD. Low EF is <45%.
*P < 0.01 for diabetic vs. nondiabetic patients within the same sex.
†P < 0.05 for diabetic vs. nondiabetic patients within the same sex.

fect of diabetes on mortality risk in women.

When analyses were restricted to blacks only, comparing diabetic with nondiabetic patients, the multivariate-adjusted RR of death was 0.86 (95% CI 0.56–1.30) for men and 1.79 (95% CI 1.12–2.87) for women, respectively—similar to findings for all races combined. The greater impact of diabetes on women also was evident in nonblacks. The corresponding adjusted RR was 0.85 (95% CI 0.38–1.89) and 2.45 (95% CI 0.58–10.39) for men and women, respectively. Because of the small numbers of deaths, especially in women (n = 10), a wider CI was obtained.

Table 3 also demonstrates that both age-adjusted and multivariate-adjusted RR for women compared with men in patients without diabetes was <1.0, consistent with the expectation that women experience a survival advantage in the absence of diabetes. In the presence of diabetes, however, the risk of death in women relative to men was reversed, indicating the higher hazard associated with diabetes in women. The risk of death from all causes and cardiac diseases in diabetic women was comparable with that of men in general (RRs = 1.13 and 1.24, respectively).

In the Cox regression analysis, the interaction term between sex (male = 0, female = 1) and diabetes (no = 0, yes = 1) was tested to evaluate further the sex difference with respect to the prognostic significance of diabetes. The multivariate-adjusted Cox coefficient for this interaction term was 0.782 (P = 0.006) for death from all causes and 0.713 (P = 0.036) for cardiac death, resulting in a significant increase in the effect of diabetes in the female sex. The interaction terms of race, sex, and diabetes were not statistically significant for both death end points, however, indicating similar sex difference in the impact of diabetes on mortality among black and nonblack patients.

CONCLUSIONS— The findings of this study demonstrate the sex difference in the contribution of diabetes to mortality in patients with angiographically confirmed CHD. In the data from this hospital registry, women had a significant survival advantage compared with men when diabetes was absent. In the presence of diabetes, however, women lost their relative protection. The greater adverse effect of diabetes on mortality in women was apparent for cardiac diseases as well as for non-CVDs. Although this effect was diminished when other clinical factors, extent of atherosclerosis, and

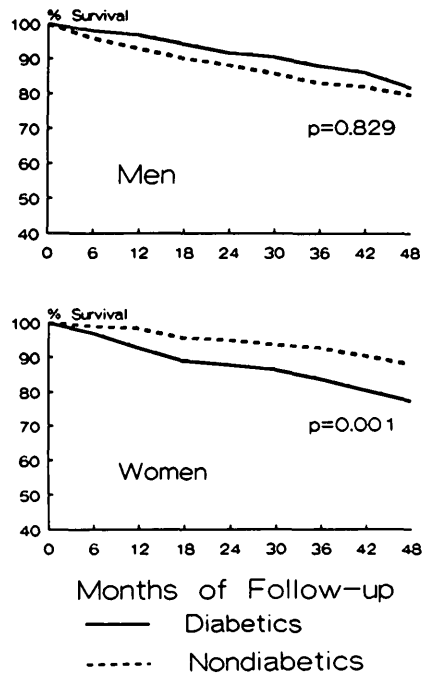

Figure 1—*Cumulative survival of patients with angiographically confirmed CHD by sex and diabetic status.*

systolic left ventricular function were taken into account, it remained present. The sex differential in mortality risk among diabetic patients appears to be present similarly in blacks and nonblacks.

Numerous prospective population-based studies (3–6) addressing diabetes as an independent risk factor in men and in women have suggested that diabetes predicts CHD mortality better in women than in men. However, no such differences were observed in other studies (8–10), including one based on a large national sample (11).

The sex differences in the impact of diabetes on patients with CHD were investigated primarily after acute MI. The effect of diabetes on in-hospital or short-term mortality is generally greater in women than men (12–16). Attempts to study differences in long-term survival in patients discharged alive have been inconclusive (15–17). Important potential limitations in studies of in-hospital patients with MI have been identified, however. Inclusion of diabetes diagnosed after a coronary event requires survival of sufficient duration for the diagnosis and could result in an artificially high survival in individuals with diabetes. If patients with less severe MI are more likely to be hospitalized because they are known to have diabetes, high apparent survival with diabetes also could result. On the other hand, a higher frequency of painless MI in diabetic patients (18), which may delay their hospitalization, could adversely affect the outcome. Also, if patients are to be studied after an MI, they must survive to hospitalization; if diabetic patients with a heart attack are more likely to die outside a hospital, those who survive may represent a subsample of diabetic patients with a favorable prognosis. This study included all inpatients and outpatients who underwent angiography and were confirmed to have CHD. Additional analyses were conducted with the exclusion of patients with acute MI. This study therefore provided an opportunity to investigate the sex-diabetes interaction in patients with well-defined CHD, a unique feature compared with other published studies.

The underlying metabolic and mechanistic derangements that link diabetes to excess risk of death in women are not fully understood. In this study, diabetic patients, compared with nondiabetic patients, were older, more likely to have hypertension, and had greater severity of coronary artery disease, especially the women. However, this study, as well as others (3–6,15,17), demonstrated that augmented risk of mortality in diabetic women cannot be totally accounted for by adverse risk factor profiles, extent of atherosclerosis, and impairment of systolic function.

Left ventricular diastolic function was not evaluated in this study. Impaired diastolic function without systolic dysfunction has been identified in several studies (19,20), and also has been related to increased mortality (21). We and others (22,23) have shown previously that heart failure with preserved systolic function is more prevalent in women, and the difference in the type of left ventricular dysfunction may be sex related. It therefore seems possible that diabetic women are particularly vulnerable to diastolic left ventricular dysfunction, and this is associated with an excess risk of mortality. The Framingham Study observed that in patients with diabetes, the age-adjusted RR of the development of cardiac failure was 2.2 for men and 5.4

Table 2— ***Causes of death in patients with angiographically confirmed CHD by sex and diabetic status***

	Men		Women	
	Diabetic (*n* = 160)	Nondiabetic (*n* = 425)	Diabetic (*n* = 155)	Nondiabetic (*n* = 234)
	Death (%)	Death (%)	Death (%)	Death (%)
All causes	41 (25.6)	110 (25.9)	47 (30.3)	39 (16.7)
Cause-specific category*				
Cardiac diseases	28 (17.5)	71 (16.7)	34 (21.9)	28 (12.0)
Acute MI	5 (3.1)	12 (2.8)	17 (11.0)	6 (2.6)
CHD	22 (13.8)	47 (11.1)	26 (16.8)	22 (9.4)
Infection	5 (3.1)	7 (1.6)	4 (2.6)	1 (0.4)
Renal failure	3 (1.9)	3 (0.7)	6 (3.9)	2 (0.9)
Non-CVD	13 (8.1)	36 (8.5)	12 (7.7)	9 (3.8)

*Based on the multiple cause-of-death classification; a patient may therefore be listed more than once.

Table 3— *RR and 95% CI of death from all causes and cardiac diseases by Cox's regression analyses*

	All causes of death		Cardiac death	
	Age-adjusted RR (95% CI)	Multiple-Adjusted* RR (95% CI)	Age-adjusted RR (95% CI)	Multiple-adjusted* RR (95% CI)
Diabetic vs. nondiabetic				
Men	0.93 (0.65–1.34)	0.85 (0.59–1.22)	1.00 (0.64–1.56)	0.88 (0.56–1.38)
Women	1.99 (1.30–3.05)	1.80 (1.16–2.79)	1.96 (1.19–3.24)	1.80 (1.07–3.02)
Women vs. men				
Nondiabetic	0.57 (0.39–0.82)	0.61 (0.41–0.89)	0.64 (0.41–0.99)	0.69 (0.44–1.09)
Diabetic	1.30 (0.85–1.98)	1.20 (0.77–1.87)	1.39 (0.84–2.29)	1.32 (0.78–2.23)
Diabetic women vs. all men	1.19 (0.85–1.66)	1.13 (0.80–1.60)	1.33 (0.89–1.97)	1.24 (0.82–1.88)

Adjusted for race, age, BMI, medical history of MI, hypertension, number of diseased vessels, and EF.

for women compared with the nondiabetic population (3). This finding led to studies suggesting a specific form of heart disease in diabetic patients, resulting from abnormalities of the small blood vessels and the myocardial interstitium (21,24). Much remains to be elucidated about the sex differences in the occurrence and natural history of this specific heart disease of diabetes and its interaction with coronary artery atherosclerosis and size of coronary artery, which is known to be smaller in women.

It has been suggested that HDL cholesterol levels are lower in diabetic women compared with diabetic men, which may explain, in part, their increased risk of heart disease (25). Lipoproteins were measured in a subsample of our cohort at baseline (46%). Women with diabetes did indeed have lower HDL levels compared with women without diabetes (36.7 vs. 40.4 meq/L, $P < 0.05$), and no differential was found in a similar comparison between men (34.7 vs. 33.3 meq/L, NS). Differences in HDL levels therefore could play a role in the sex difference in the impact of diabetes on mortality.

The contribution of obesity to diabetes complications and mortality is controversial (12–14,18,26,27). In this study, obesity was more prominent in women patients with diabetes than those without the condition. No significant adverse effect of increased BMI on the prognosis of either diabetic men or women was found (data not shown). It appears that obesity in diabetic women cannot explain the excess risk of mortality. Other hypotheses, including insulin-androgen interaction (6) and sex differences in the hypercoagulable state associated with diabetes (28) need to be evaluated further.

Note that the definition of diabetes was limited to a history of diabetes diagnosed by a physician. We cannot directly ascertain whether these diabetic patients would be so classified by currently established criteria. Some studies suggest that about 14–15% of self-reported diabetes may not meet National Diabetes Data Group Criteria (29). Another limitation is that ~50% of all adults who have diabetes are not diagnosed (29). Data from the second NHANES (29) suggest that women 45–64 yr of age are somewhat more likely to have undiagnosed diabetes than men. These asymptomatic diabetic patients, if misclassified as nondiabetic, should render the null hypothesis more likely. Considering this, the excess risk of death in diabetic women may actually be greater than that reported in this study.

Women are usually less vulnerable to CHD than men in Western industrialized countries and live longer than men. However, once overt CHD becomes clinically manifest, women tend to lose their earlier natural advantage. Diabetes has an additional important impact on women, independent of the extent of coronary artery atherosclerosis and other clinical variables. The beneficial effect of therapy for diabetes, in terms of morbidity and mortality, has not been well defined. However, when CHD appears, the potential benefit of good control of the diabetic condition assumes added importance, particularly in women, where the effect of diabetes to increase mortality is considerable.

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