Sex Differentials in Predictors of Mortality for Patients With Adult-Onset Diabetes

A population-based follow-up study in Beer-Sheva, Israel

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OBJECTIVE — To test the hypothesis that factors predicting mortality differ between diabetic men and women.

RESEARCH DESIGN AND METHODS — A total of 498 known patients with diabetes residing in a well-defined geographical area and receiving primary health care in 3 primary care community clinics were interviewed and examined between 1988 and 1990.

RESULTS — By 31 July 1998, after a mean follow-up period of 7.8 years, 148 patients (68 men and 80 women) had died (29.7%). No statistical differences in survival rate or in the specific causes of death were found between men and women. In the univariate analysis of factors examined at baseline, GHb levels were significantly higher among women who died compared with women who survived, but this was not the case for men. Conversely, a trend of higher triglyceride and uric acid levels was found for men who died compared with men who survived, but this was not the case for women. Multivariate Poisson regression analysis showed significantly higher risk ratios for mortality in men ≥63 years of age, men with microalbumin excretion ≥30 mg/l, and men with higher triglyceride levels. In contrast, the analysis in women showed that higher GHb and creatinine levels and a reported history of heart disease were the only factors at the baseline examination significantly and independently associated with an increased risk ratio of mortality.

CONCLUSIONS — The results suggest the existence of sex-specific interactions with various metabolic factors associated with diabetes that may have a different effect on mortality for each sex.

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The increased risk of mortality in diabetic patients compared with that of nondiabetic individuals has been reported in different populations (1–8). Although some of these studies described sex differences in specific cardiovascular risk factors that may account for differences in cardiovascular mortality (4,6), little attention has been given to the possibility that factors predicting overall mortality could vary between diabetic men and women. Moreover, in the few studies in which data were analyzed separately for each sex, the results were contradictory (7,9,10).

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Abbreviations: SMR, standardized mortality rate.

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

The Beer-Sheva Diabetes Study, a population-based follow-up study of a cohort of all known adult-onset diabetic individuals in a defined geographical area, allowed the testing of the hypothesis that factors related to mortality may differ between men and women.

RESEARCH DESIGN AND METHODS

All known diabetic patients diagnosed at ≥30 years of age from 3 primary care health centers who belong to the largest health insurance fund in Israel (Kupat Holim Clalit, which covered ~85% of the population in 1988) were identified between 1988 and 1990 in Beer-Sheva, Israel. The total population of persons ≥30 years of age in the clinics was 10,600 in 1988.

Ascertainment of diabetes

Diabetic patients were identified by physician-generated lists of all known diabetic individuals in their practices who were diagnosed at ≥30 years of age and by a complete medical record review of all persons ≥30 years of age registered in the 3 primary care health centers. The record review was carried out by a trained epidemiologist (L.M.Z.) who was unaware of the list of patients provided by physicians.

For the record review, diabetes was defined by the presence of any of the following criteria: *1*) a diagnosis written in the medical record, *2*) the recording of 2 consecutive fasting plasma glucose levels of ≥7.8 mmol/l (140 mg/dl) according to the World Health Organization criteria (11), and *3*) the recording of any hypoglycemic therapy (including diet).

Baseline data collection

An invitation letter to the clinic was mailed to all identified patients. After giving written consent, patients were interviewed about their demographic characteristics and their history of comorbid conditions. In addition, 2 standardized blood pressure measurements recorded to the nearest even digit with a Baum sphygmomanometer were

Table 1—*Diabetes-related characteristics of the study population by sex*

Characteristic	Men	Women	*P*
n	233	265	—
Age (years)	62.4 ± 10.6	62.3 ± 9.9	0.95
Age at diagnosis (years)	53.8 ± 11.1	52.5 ± 11.0	0.19
Duration of known diabetes (years)	8.5 ± 7.8	9.8 ± 7.8	0.07
Treatment at baseline			
Diet alone	35.2	34.0	0.32
Oral hypoglycemic agents	57.5	55.8	—
Insulin	6.0	6.8	—
Insulin plus oral hypoglycemic agents	1.3	3.4	—

Data are *n*, means ± SD, or %.

obtained. The mean of the 2 readings was used for analysis. BMI (weight in kilograms/height in meters squared) was calculated, and an eye examination including visual acuity and direct and indirect ophthalmoscopy was carried out by an ophthalmologist with special expertise in retinal disorders. For laboratory testing, blood was drawn in the morning after at least 8 h of fasting, and samples were shipped the same morning to the central laboratory. Plasma glucose, serum creatinine, uric acid, serum cholesterol, and triglyceride levels were estimated the same day by using an automated method (SMA) at the central laboratory of the Soroka University Medical Center. GHb was measured by using affinity chromatography (Glycaffin; Isolab, Akron, OH) with a normal range of 4–8%. In addition, the first morning urine void was collected for determination of microalbumin and protein excretion. Urinary quantitative (for micro- and macro-) albumin excretion was determined in duplicates by using radioimmunoassay. This study was approved by the institutional review board.

Death ascertainment

The vital status of the cohort was ascertained up to 31 July 1998 by using the computerized population register file of the Ministry of Interior. Causes of death coded according to the *International Classification of Diseases and Causes of Death, Ninth Revision,* were obtained from the Central Bureau of Statistics.

Statistical analysis

Standardized mortality rates (SMRs) were computed to estimate the observed/expected number of deaths in the diabetic cohort compared with the population of Beer-Sheva by using the age distribution of the Beer-Sheva population in 1990 provided by the Central Bureau of Statistics (12). Sex- and age-specific Kaplan-Meier survival curves were obtained and were tested for statistical significance by using the log-rank statistic.

Student's *t* test, the χ^2 test, and Fisher's exact test were used for univariate statistical analyses. The risk ratio of mortality for the various factors at baseline was estimated by using multivariate Poisson regression analysis with the EGRET statistical package (13). To ensure that we had enough individuals in each age-group, the population was divided into 2 age-groups (<63 and ≥ 63 years) according to the median of the age distribution of the entire population (which was similar for both sexes). Triglyceride levels were further divided into deciles for multivariate analysis. P values of ≤ 0.05 were considered to be of statistical significance.

RESULTS — A total of 568 diabetic patients ≥ 30 years of age were identified between 1 January 1988 and 30 May 1990. Of them, 498 subjects (87.7%) agreed to participate in the study and underwent the baseline examination. No statistically significant differences were evident between participants and nonparticipants regarding age, sex, and diabetes management as recorded in the medical record.

Table 1 shows selected diabetes-related characteristics for men and women. Age, age at diagnosis, and current treatment were similar for both sexes. Duration of known diabetes was slightly greater in women than in men.

Vital status was ascertained in all participants as of 31 July 1998. A total of 148 patients (29.7%) died (68 men and 80 women) during a mean ± SD follow-up period of 7.8 ± 2.4 years, which represents 3,853.5 person-years of observation. The SMR of diabetic patients compared with the Beer-Sheva population was 1.85 for men and 1.27 for women. No statistically significant differences in the Kaplan-Meier survival analysis were found between men and women in the 2 age-groups. Causes of death were available for 60 men (88.2%) and 71 women (88.7%). In 8 men and 9 women, the cause of death was not available because death occurred outside of the Beer-Sheva region. As expected, acute and chronic ischemic heart disease was the most prevalent cause of death and accounted for 35.3% of deaths in men and 33.8% of deaths in women. Cerebrovascular disease accounted for 5.9% of deaths in men and 10.0% of deaths in women. No statistically significant differences were found between sexes regarding causes of death. Tables 2 and 3 show differences in baseline characteristics between patients who died and those who survived for both sexes. Sur-

Table 2—*Differences by sex in baseline characteristics between patients who died and those who survived*

	Men (*n* = 233)			Women (*n* = 265)		
Characteristic	Dead	Alive	*P*	Dead	Alive	*P*
n	68	165	—	80	185	—
Age (years)	68.9	59.7	<0.0001	67.2	60.2	<0.0001
Duration of known diabetes (years)	10.7	7.6	0.013	12.1	8.8	0.002
Systolic blood pressure (mmHg)	152.0	142.5	0.002	159.0	147.6	<0.0001
Diastolic blood pressure (mmHg)	83.9	84.0	0.98	83.2	82.8	0.80
BMI (kg/m^2)	27.7	27.3	0.52	29.9	29.6	0.74
Current smokers (%)	20.6	28.5	0.21	12.7	15.4	0.57
Reported heart disease (%)	52.9	23.6	<0.0001	47.5	22.2	0.00003
Reported kidney disease (%)	11.8	10.3	0.74	11.3	8.1	0.41
Diabetic retinopathy	34.8	18.4	0.007	35.4	20.1	0.008

Data are *n*, means, or %.

Table 3—*Differences by sex in biochemical baseline characteristics between patients who died and those who survived*

Characteristic	Men (n = 233)			Women (n = 265)		
	Dead	Alive	P	Dead	Alive	P
n	68	165	—	80	185	—
Fasting plasma glucose (mmol/l)	9.56	9.97	0.46	10.4	9.77	0.12
GHb (%)	10.8	10.9	0.78	12.0	10.6	0.003
Total cholesterol (mmol/l)	5.51	5.72	0.28	6.52	6.30	0.26
Triglycerides (mmol/l)	2.36	2.01	0.14	2.40	2.20	0.37
Serum creatinine (mg/dl)	1.06	0.98	0.015	0.97	0.79	0.009
Uric acid (mg/dl)	6.04	5.69	0.10	5.41	5.49	0.70
% with microalbumin ≥30 mg/l	46.3	15.9	0.0001	39.3	16.2	0.0003

Data are n, means, or %.

vivors were significantly younger, had diabetes of shorter duration, had a lower prevalence of microalbuminuria (≥30 mg/l), had retinopathy, and had self-reported heart disease. In addition, their mean systolic blood pressure and serum creatinine levels were significantly lower than those of deceased patients. However, differences in some characteristics between survivors and patients who died were found in one sex but not in the other. Men who died had higher (although not statistically significant) triglyceride and uric acid levels. Women who died had significantly higher GHb levels than women who survived. Among men, GHb values were not different between survivors and patients who died.

Multivariate Poisson regression analyses were performed separately for men and for women, including variables that were statistically significant in the univariate analysis and variables known to be risk factors. The same list of variables was used in the analysis for both sexes.

Tables 4 and 5 display the results of these analyses. In men, microalbumin excretion of ≥30 mg/l, age at baseline of ≥63 years, and triglyceride levels were significantly associated with the risk of death. In women, self-reported heart disease, serum creatinine levels, and GHb levels were the only significant factors related to an increased risk of death. The addition of BMI, total cholesterol, diabetic retinopathy, smoking, and mode of therapy (insulin or other) to the statistical models did not affect the results.

CONCLUSIONS

— The main finding of this study is the difference between diabetic men and women regarding factors related to an increased risk of mortality for a mean follow-up period of >7 years. In contrast, no differences between sexes were found in rates of survival or in causes of death. Although microalbumin excretion of ≥30 mg/l was significantly more prevalent for both sexes at baseline among patients who subsequently died, its specific contribution to mortality was observed only in men. Age and triglyceride levels were also related to the increased risk ratio of mortality only in men. In women, GHb levels, serum creatinine levels, and self-reported heart disease were the only factors related to increased risk ratios of mortality. Surprisingly, little data are available on sex differences regarding predictors of mortality in diabetic individuals. Barrett-Connor and Wingard (6) described sex differences in mortality from ischemic heart disease among diabetic individuals and showed that male sex made a significant contribution to the prediction of fatal ischemic heart disease. Marrugat et al. (14) found, in a cohort of patients after acute myocardial infarction, that diabetes was an independent risk factor for long-term mortality in women. Greenland et al. (15) and Benderly et al. (16) reported that diabetes was a major factor related to long-term mortality after myocardial infarction in women but not in men. Kimmelstiel and Konstam (17), in a review of heart failure in women, reported that women seemed more likely than men to exhibit heart failure after a myocardial infarction. Savage et al. (9) found that the high mortality rate among diabetic women was attributable to their increased risk of severe congestive heart failure and cardiogenic shock. Possibly some of these explanations could account for the fact that, in our study, self-reported history of heart disease at the baseline examination was related to mortality in women but not to mortality in men.

To our knowledge, microalbuminuria has been recognized as a risk factor for mortality in various populations, but sex differences have not been reported previously (18–21). Therefore, extrapolating our finding of the selective prediction of microalbuminuria for mortality only among men is difficult until this observation is replicated in other studies.

High triglyceride levels as an independent risk factor of mortality in diabetic patients have been previously reported, although the effect of triglyceride levels has not been estimated separately in each sex (22,23). In these studies, data were analyzed adjusting for sex, and therefore the specific contribution of sex could not be estimated.

Another sex difference in our study is the finding of GHb levels being related to subsequent mortality only in women. The univariate analysis showed that women who survived had significantly lower plasma glucose and GHb levels at baseline

Table 4—*Poisson regression analysis of factors related to the risk of mortality in diabetic men*

Factor	Coefficient	Rate ratio	P
Microalbumin (≥30 vs. <30 mg/l)	1.272	3.57	0.002
Age (≥63 vs. <63 years)	1.164	3.20	0.008
Triglycerides (deciles)	0.153	1.17	0.015

Table 5—*Poisson regression analysis of factors related to the risk of mortality in diabetic women*

Factor	Coefficient	Rate ratio	P
GHb (continuous)	0.193	1.21	0.007
Serum creatinine (continuous)	0.916	2.50	0.022
Reported history of heart disease (yes/no)	1.256	3.51	0.001

than those who died, but these values were not different from those of the men (both survivors and deceased), which suggests that poor diabetes control may be a more important prognostic risk factor for mortality in women than in men. Muggeo et al. (10) reported that, for the large cohort of the Verona Diabetes Study, mean fasting plasma glucose levels in the top tercile were predictors of mortality in elderly diabetic women but were not predictors in men. In another study, Scheidt-Nave et al. (24) described unexplained sex differences regarding the effect of fasting glycemia on mortality from ischemic heart disease among nondiabetic individuals.

Our study hypothesis was that predictors of mortality in diabetic patients may differ between men and women; therefore, data were analyzed separately for each sex. The findings of the univariate analysis showed sex differences between survivors and patients who died in some of the baseline attributes. These findings justified the performance of sex-specific analyses rather than the use of sex-adjusted multivariate analyses, which could neutralize the effect of sex on some of the explanatory variables.

In summary, the results of our population-based study show that the overall risk of mortality (and causes of death during a mean follow-up period of almost 8 years) is similar for diabetic men and women. However, factors predicting mortality differed between the sexes, which suggests that diabetes control and concurrent conditions (hypertriglyceridemia, high blood pressure, and heart disease) may have a different effect on diabetic men and women. Moreover, if replicated, these findings may have important implications for defining more specific therapeutic goals in the management of diabetes and related morbidity in each sex.

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