Mortality of Mexican Americans With NIDDM

Retinopathy and other predictors in Starr County, Texas

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OBJECTIVE— To determine the rate and risk factors of mortality in a cohort of Mexican Americans with NIDDM.

RESEARCH DESIGN AND METHODS— A cohort of 353 Mexican Americans with NIDDM were identified between 1981 and 1986. All individuals underwent extensive evaluations that included physical, historical, ophthalmological, and laboratory assessments. This cohort was followed prospectively for a mean of 8 yr. Follow-up included mortality surveillance, death certificate extraction, and a combination of annual and intermediate examinations.

RESULTS— The cohort experienced 67 mortality events. One-third of all deaths were premature <65 yr of age) and most often were attributed to diseases of the heart (60.0%). In no case was diabetes listed as the cause of death, although it was listed as a contributing cause in 25.5% of cases. Men had a higher mortality rate than women. In both sexes, baseline retinopathy was identified as an important predictor of subsequent mortality. Mortality was significantly elevated in those with nonproliferative retinopathy and even further elevated in those with proliferative disease (relative risks of ≥4 for proliferative disease).

CONCLUSIONS— Mexican Americans with NIDDM are experiencing premature and excessive mortality compared with the general population. The results clearly link microvascular complications with macrovascular disease, but this link is not explained by a more untoward profile of traditional cardiovascular risk factors. Retinopathy appears to serve as an important monitor of the progression of diabetes and when identified would warrant aggressive action to inhibit or slow the processes leading to subsequent mortality.

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NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; ETDRS, EARLY TREATMENT OF DIABETIC RETINOPATHY STUDY; IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; BMI, BODY MASS INDEX; ANCOVA, ANALYSIS OF COVARIANCE; SMR, STANDARDIZED MORTALITY RATIO; CI, CONFIDENCE INTERVAL; HDL, HIGH-DENSITY LIPOPROTEIN.

Ultimately, the impact of diabetes is reflected in increased morbidity and premature mortality. Numerous studies have documented the morbidity associated with diabetes, but mortality investigations have been more limited because of the weaknesses inherent in vital records. Even so, these data demonstrate the influence of diabetes on mortality. In the U.S., 1.8% of all death certificates list diabetes as the cause of death, placing it among the top 10 causes of mortality (1). It has been estimated that life expectancies of men and women with diabetes are reduced by 9.1 and 6.7 yr, respectively (2). Undoubtedly, the mortality rates are gross underestimates because of the known lack of reporting of diabetes as a cause of death. Reviews of death certificates of individuals known to have diabetes have shown that 33–66% do not list diabetes among the causes of death (3–5).

Hispanics in general, and Mexican Americans in particular, are affected with NIDDM severalfold more frequently than the general population (6–11). Mortality statistics tend to parallel this pattern. In Texas, like the U.S. population, 1.8% of all death certificates listed diabetes as causative over the period 1970–1989 (12). However, examination of county-specific diabetes mortality in Texas demonstrates notable fluctuations and geographic clustering with the highest diabetes-specific mortality occurring in those southern Texas counties that have substantial Mexican-American populations (7,12). Of the 163 Texas counties experiencing ≥2,000 total deaths over the past two decades, Starr County has had the highest diabetes-specific mortality (4.5%) (12). Such figures do not document the true diabetes mortality nor do they provide insights into the causes of death among those with diabetes and the risk factors for mortality. This type of information can only come from prospective mortality surveillance on representative and characterized cohorts. Such studies are rare in the general pop-

ulation and are virtually nonexistent for Mexican Americans with NIDDM. In this investigation, we describe the mortality experience of a cohort of 353 Mexican Americans with NIDDM.

RESEARCH DESIGN AND METHODS

— From 1981 to 1983, a population screening was performed in Starr County, TX, to identify individuals with NIDDM and their families. The screening methods were described previously (7). Briefly, blocks were randomly selected from each of the three main communities in Starr County in proportion to town size. All individuals in each dwelling unit ≥15 yr of age were screened for diabetes with a sequential procedure. Where unequivocal classification of diabetes could not be made based on previous diagnosis and current treatment or a series of blood glucose determinations, oral glucose tolerance tests were administered. A total of 2498 individuals were enumerated, of whom 77.3% participated. Participants identified as having diabetes (131) and their first- and second-degree relatives were invited to a complete physical evaluation in our field office. A total of 1509 individuals underwent the evaluation, including 278 people with diabetes.

The examinations included resting electrocardiogram; physical evaluation; anthropometric assessment; medical, medication, diabetes, and cardiovascular histories; ophthalmologic assessment; and laboratory evaluations. The ophthalmological examination for those with diabetes included measurement of visual acuity, administration of mydriatics, slit-lamp examination, direct and indirect ophthalmoscopy, and fundus photography of seven standard fields according to protocols established in the ETDRS (13). Retinopathy status was scored based on ETDRS classifications by certified readers. A subsequent investigation in Starr County conducted from 1984 to 1986 also sampled blocks in the three major communities. In this study, one randomly selected individual aged 15–74 yr from each household on selected blocks was invited for a complete evaluation. First-degree relatives of individuals with gallbladder disease and similar relatives for an age, sex, and town-matched control (no gallbladder disease) were also invited for examination. Participation in the random phase of this study was 73.2%. The first 82 individuals examined who had diabetes were added to the previous cohort of 278 to increase the statistical power of follow-up investigations. The evaluation used in this study used protocols similar to those above except that the initial physical evaluation did not include ophthalmological examinations (14).

In the fall of 1986, these 360 individuals were enrolled in a prospective investigation of the development of complications of diabetes. Reevaluations began in January 1987 and consisted of a series of complete annual examinations (including fundus photography) and intermediate in-home evaluations. The purpose of the annual examinations was to characterize fully the health status of all participants, while the intermediate examinations were to provide a near-continuous picture of metabolic control. Of the 360 individuals, 7 were classified as having IDDM based on a diagnosis before 40 yr of age, BMI <30 kg/m^2, and continuous use of insulin since diagnosis (15). These individuals have been excluded from all subsequent considerations in this paper.

Mortality status of this cohort of 353 individuals with NIDDM has been updated continuously through interviews, telephone conversations, obituary reviews, and reviews of death certificates. Even for those who have moved, it has been possible to ascertain status through telephone contact or interviews with relatives residing in Starr County. For each mortality event, all primary and secondary causes of death were extracted from available death certificates. All causes were then classified according to ICD-9-CM codes by a single reviewer (16). For those individuals for whom death certificates could not be obtained because of distance (e.g., 5 occurred in Mexico) or recency of event, cause of death was determined through interviews with family members by local field staff members.

Various statistical techniques were used to determine those factors predictive of subsequent mortality. These ranged from calculation of risk ratios to analysis of survival times with covariates that used proportional hazards regression models (17). Because of apparent differences by sex, most analyses were conducted for men and women separately. In all instances, age was included in the proportional hazards models as a covariate. Estimates of survival curves among retinopathy groups were obtained by using the nonparametric Kaplan-Meier method (17). ANCOVA techniques (18) were used to determine the significance of mean differences in putative risk factors among survival classifications. All analyses were performed as implemented in STATA (19).

RESULTS

— As of 31 March 1992, each member of the cohort of 353 NIDDM individuals had been followed for an average 8 yr with a total of 2834 person-yr of follow-up. Of the 353 individuals, 222 are women and 131 men. Mean ages of onset of NIDDM for men and women, respectively, were 47 and 50 yr (P = 0.064). This cohort has experienced 67 mortality events (30 women, 37 men). Of these, 22 are classified as premature deaths (death <65 yr of age) and result in 145 yr of potential life lost. Death certificates were extracted for 55 events, and cause of death was determined for the remaining 12 based on family interviews. Table 1 summarizes these data. The table is ordered according to the 10 leading causes of death in the US for 1988 (20). Focusing on only the death certificate results (those values not in parentheses), it is seen that 60% of all deaths among this cohort were attributed to diseases of the heart. In 72.7% of the deaths, diseases of the heart are listed

Table 1—*Causes of death among Mexican Americans with NIDDM based on death certificate review*

Cause of death (ICD-9-CM codes)	U.S. population	Deaths in Starr County individuals with NIDDM			
		Primary cause of death		Primary or contributing cause	
	Percent of total deaths	*N*	Percent of total	*N*	Percent of total
Heart disease (390–398, 402, 404–429)	35.3	33 (36)	60.0 (53.7)	40	72.7
Malignant neoplasms (140–208)	22.4	3 (4)	5.5 (6.0)	4	7.3
Cerebrovascular disease (430–438)	6.9	7 (7)	12.7 (10.4)	13	23.6
Accidents (E800–E949)	4.5	0 (4)	0 (6.0)	0	0
COPD (490–496)	3.8	0 (0)	0 (0)	1	1.8
Pneumonia and influenza (480–487)	3.6	0 (0)	0 (0)	0	0
Diabetes mellitus (250)	1.9	0 (2)	0 (3.0)	14	25.5
Suicide (E950–E959)	1.4	1 (1)	1.8 (1.5)	1	1.8
Liver disease (571)	1.2	0 (0)	0 (0)	2	3.6
Nephritis (580–589)	1.0	1 (2)	1.8 (3.0)	6	10.9
All other	18.0	10 (15)	18.2 (22.4)	30	54.5

Numbers in parentheses include both death certificate results and interview results.

as either the primary or contributing cause. Of the 33 cases listing diseases of the heart as the primary cause, 9 were classified as being attributable to coronary heart disease (ICD-9-CM codes 410.0–411.8, 412–414.9, and 798.1 [21]). As a primary or contributing cause, coronary heart disease was present in 25 of 40 death certificates listing diseases of the heart. In no case was diabetes listed as the primary cause of death, but it did appear as a contributing cause in 25.5% of the cases. Cerebrovascular disease and nephritis were the other main contributors to mortality identified on death certificates in this cohort.

The prospective nature of this investigation permits assessment of those factors at baseline that predict subsequent mortality. Table 2 enumerates basic descriptive statistics stratified by survival category for the major risk factors evaluated. All values represent means except for sex and smoking, where proportions are given. As is evident, those not surviving were more likely to be older, male, and to have had diabetes longer. Analyzing age, sex, and duration with the Cox proportional hazards model demonstrated that all three factors are significant predictors of survival time ($P = 0.000$, $P = 0.027$, and $P = 0.040$, respectively). When sexes were analyzed separately, however, duration was only significant in women ($P = 0.026$; $P = 0.301$ in men) suggesting a duration by

Table 2—*Baseline values categorized by survival status*

	Survived		Died	
	N	Mean ± SD	*N*	Mean ± SD
Age (yr)	286	53 ± 12.2	67	64 ± 9.7
Men	94 (32.9%)		37 (55.2%)	
Duration (yr)	285	5.9 ± 6.5	67	9.6 ± 9.6
BMI (kg/m^2)	282	31.0 ± 5.5	63	28.3 ± 4.4
Glucose (mM)	282	10.6 ± 3.99	66	10.6 ± 4.22
HbA_1 (%)	271	10.7 ± 3.1	59	10.8 ± 3.3
Cholesterol (mM)	270	5.4 ± 1.03	58	5.5 ± 1.24
HDL (mM)	268	1.09 ± 0.311	57	1.06 ± 0.324
Systolic blood pressure (mmHg)	284	142 ± 21.8	66	145 ± 24.6
Diastolic blood pressure (mmHg)	284	80 ± 11.5	66	79 ± 12.7
Current smoker	61 (22.1%)		11 (18.3%)	
Age at death (yr)	—		67	69 ± 10.0

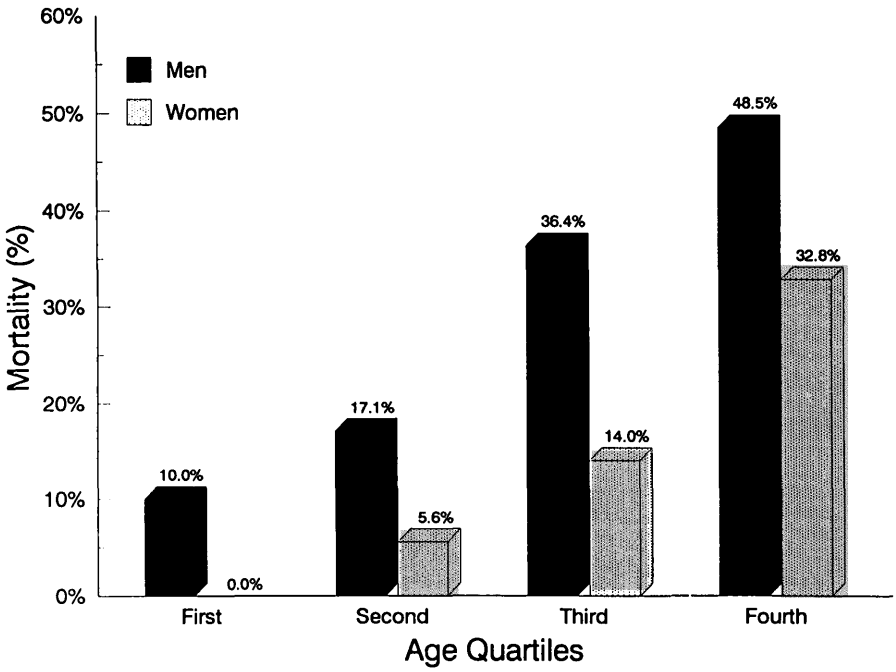

Figure 1—*Effects of age and sex at baseline on subsequent mortality among Mexican Americans with NIDDM. Age quartile cut points were 49, 58, and 67 yr in men and 45, 54, and 62 yr in women.*

sex interaction. Further analysis failed to reject the null hypothesis of no duration by sex interaction ($P = 0.270$). Because of the suggested effect and the marked difference in mortality rate by sex, subsequent analyses were conducted separately for men and women as a conservative approach. The age and sex effects are illustrated in Figure 1. Blood glucose, HbA_1, and the other quantitative factors were remarkably similar between the two groups. Both groups were comparable with regard to medication use with 26 and 31% using insulin at baseline among survivors and nonsurvivors, respectively. Similarly, 54 and 61% of each group, respectively, were taking oral hypoglycemic agents at baseline.

Baseline ophthalmological examinations (including fundus photography) were completed on 321 individuals. Classification of retinopathy was made on the basis of the fundus photographs. Of the 321, 199 were classified as having no diabetic retinopathy. Among the 122 that had retinopathy (61 men, 61 women), 31% were classified as having proliferative diabetic retinopathy (36.1% in men, 26.2% in women).

Mortality among the three retinopathy groups (none, nonproliferative, and proliferative) was 13.1, 21.4, and 39.5%, respectively. The pattern was consistent in both men and women and is illustrated in Fig. 2. To determine whether this step function of mortality was simply attributable to a correlation of retinopathy with age, sex, and duration of diabetes, survival time was again analyzed by using proportional hazards models. These results are summarized in Table 3. In both men and women, a clear and consistent predictive effect of background retinopathy and proliferative retinopathy on subsequent mortality is apparent, but duration is no longer significant in either sex. This likely reflects the fact that retinopathy captures a portion of the duration information because duration is a predictor of retinopathy. Repeating the analyses without du-

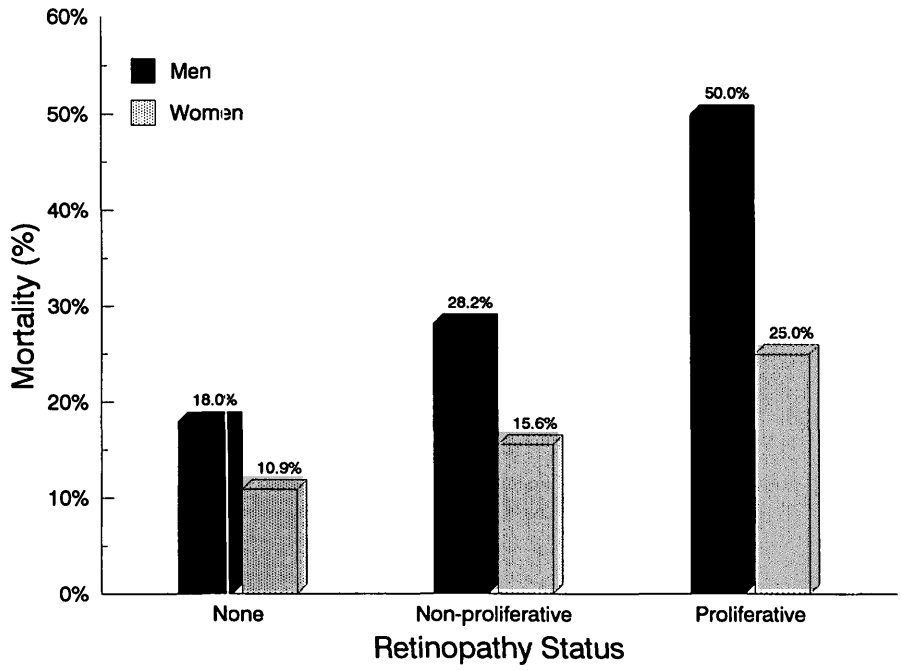

Figure 2—*Effects of retinopathy status and sex on subsequent mortality among Mexican Americans with NIDDM in Starr County, TX.*

Table 3—*Proportional hazards model, including the effects of age, duration, background retinopathy, and proliferative retinopathy stratified by sex*

	Women				Men			
Variable	Coefficient	SE	T	P > (T)	Coefficient	SE	T	P > (T)
Age	0.124	0.022	5.75	0.000	0.049	0.017	2.96	0.004
Duration	0.018	0.022	0.80	0.427	0.010	0.020	0.49	0.625
Background retinopathy	1.147	0.525	2.19	0.030	0.894	0.445	2.01	0.047
Proliferative retinopathy	1.238	0.677	1.83	0.069	1.343	0.444	3.03	0.003

ration makes the association of mortality with retinopathy even more evident. In men, the coefficients associated with background and proliferative retinopathy are 0.937 ($P = 0.033$) and 1.385 ($P = 0.002$), respectively. The corresponding figures for women are 1.253 ($P = 0.014$) and 1.488 ($P = 0.013$). The coefficients for proliferative retinopathy translate into relative risks of ≥4 (4 in men, 4.4 in women). Kaplan-Meier survival probability plots are provided in Fig. 3 to illustrate the marked effect of retinopathy on mortality experience.

In addition to retinopathy as a predictor of mortality, separate analyses were performed considering all previous potential risk factors. Each sex-specific analysis included age and duration of diabetes as covariates and one of the additional risk factors enumerated in Table 2 (e.g., glucose). In men, none of these other factors were significant or even suggestive (i.e., $P < 0.10$) predictors of subsequent mortality. The analysis of women, on the other hand, identified cholesterol ($P = 0.003$), diastolic blood pressure ($P = 0.050$), and insulin use ($P = 0.079$) as potential predictors of mortality. Analyzing these factors in women while including retinopathy, age, and duration in the model gave equivocal results (Table 4). Age continued to be significant, but only cholesterol remained significant ($P = 0.034$) in the presence of these other factors. In fact, any time retinopathy and cholesterol are included in the model in women, an attenuation of significance exists, suggesting a correlation between these factors. Further analysis showed that cholesterol was a significant predictive factor of proliferative retinopathy in women and hence, like duration, retinopathy is likely reflecting some of this effect.

CONCLUSIONS— According to the 1990 U.S. census, Starr County has a population of 40,518 individuals, of whom 97.2% were classified as Hispanic (almost entirely Mexican American). Starr County is known to have rates of NIDDM that are severalfold higher than the general U.S. population (7). The present data document the impact of diabetes on mortality among Mexican Americans. Had this cohort experienced death rates equal to those of the general U.S. population in 1988 (20), 30 deaths would have been expected, yielding an SMR of 2.23 (95% CI 1.69–2.76). These findings are not unlike those that have been reported for non-Hispanic whites (23,24) and other populations (25). Particularly noteworthy is that fully 33% of the deaths among this cohort were premature. Key to understanding the implications of these figures is determination of cause and predictive factors of mortality.

The cause of death results clearly establish an underrepresentation of dia-

Table 4—*Proportional hazards model analysis stratified by sex and including age, duration, background retinopathy, proliferative retinopathy, cholesterol, and insulin use*

	Women				Men			
Variable	Coefficient	SE	T	P > (T)	Coefficient	SE	T	P > (T)
Age	0.142	0.025	5.71	0.000	0.050	0.018	2.88	0.005
Duration	0.039	0.031	1.28	0.202	0.021	0.022	0.99	0.325
Background retinopathy	0.186	0.648	0.29	0.774	0.888	0.487	1.82	0.071
Proliferative retinopathy	−0.111	1.032	−0.11	0.914	1.593	0.466	3.42	0.001
Cholesterol	0.561	0.262	2.14	0.034	0.045	0.179	0.25	0.801
Insulin use	0.566	0.524	1.08	0.282	−0.815	0.467	−1.74	0.084
Diastolic blood pressure	0.016	0.021	0.76	0.451	−0.001	0.020	−0.30	0.763

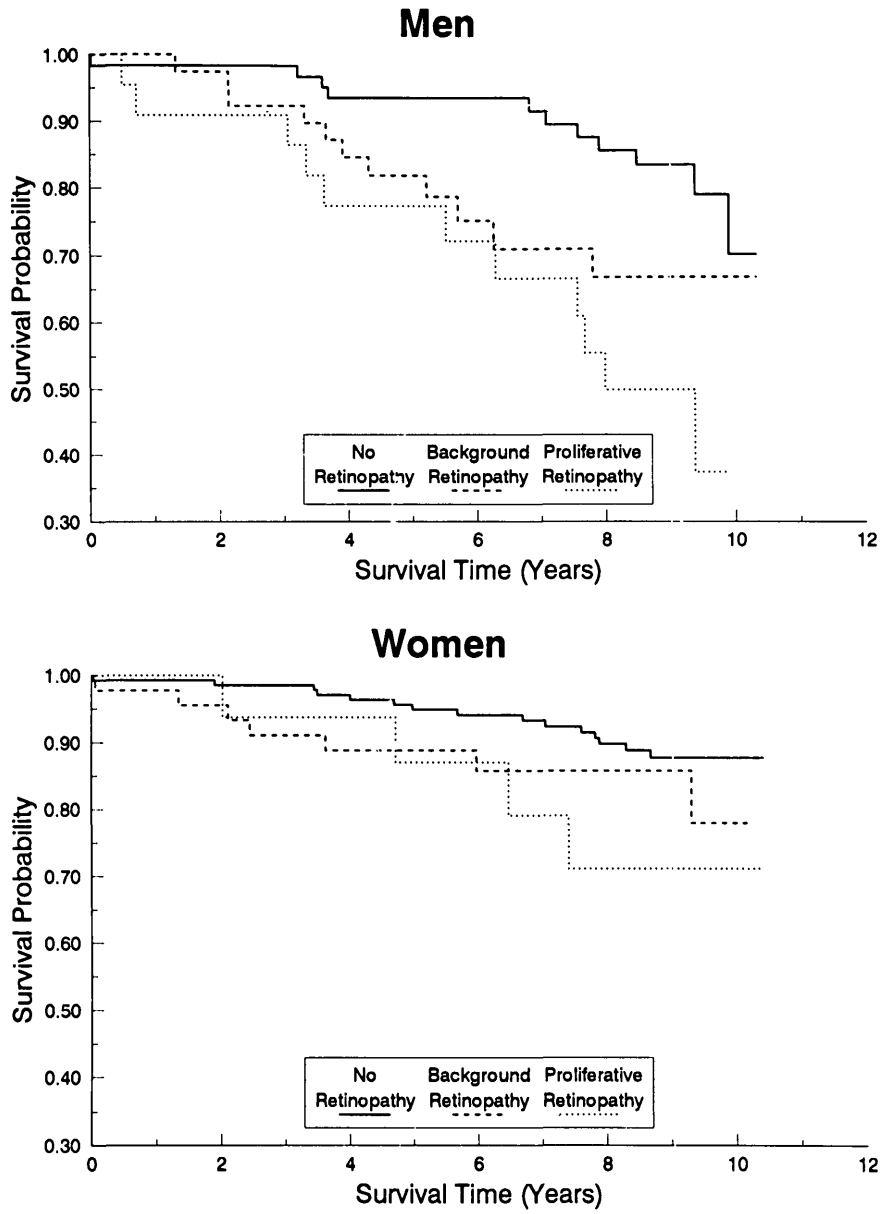

Figure 3—*Kaplan-Meier survival curves according to retinopathy status at baseline for men and women.*

betes as a cause of death among Mexican Americans with NIDDM. In 74.5% of all deaths, diabetes was not even mentioned as a contributor. Most deaths were attributed to diseases of the heart. Interestingly, the frequency of diseases of the heart were similar to what has been shown for other populations of individuals with diabetes (26–28). The observed frequencies of heart disease-related deaths in both men and women were significantly higher than would have been expected based on heart disease mortality in the U.S. population at large (20) and is largest in women. The SMRs and CIs for deaths attributed to heart disease in men and women in Starr County were 3.61 (2.10–5.11) and 4.20 (2.76–6.15), respectively. This increase, however, is not entirely explained by an increased aggregation of traditional cardiovascular risk factors, a finding that is similar to what has been shown previously (24,29). Cox proportional hazards analysis of age, cholesterol, HDL, BMI, and smoking distributions in those individuals dying from diseases of the heart versus those surviving identified age, cholesterol, and HDL as significant predictors in females. In males, only age was a significant predictor. In neither case could these factors explain the marked increase in cardiovascular mortality. The higher frequency of deaths caused by diseases of the heart may reflect the poorer prognosis for individuals with diabetes hospitalized for acute myocardial infarctions (27).

The increased cardiovascular mortality in Mexican Americans with NIDDM has other implications for the population because Hispanics in general are thought to have lower or, at least, no higher incidences of heart disease compared with the general population (30,31). From 1981 to 1986 in Starr County, 38% of all deaths listed diseases of the heart as the cause. This figure is similar to what is observed in the general population. The 60% so attributed in this cohort imply that the nondiabetic population is actually experiencing lower cardiovascular mortality to compensate for the increase among those with diabetes. A lower incidence of heart disease has been predicted for Hispanics based on Native-American admixture and the low incidence in Native Americans (32,33). The results reported here are only partially compatible with this because Native Americans with NIDDM have been shown to have lower incidences of coronary heart disease (21). Mexican Americans in Starr County also have been shown to have lipid-related profiles that are closer to the general population than to Native Americans (14). The sources of increased heart disease mortality among Mexican Americans with NIDDM remain to be elucidated.

Of perhaps most interest is the clear connection of retinopathy with subsequent mortality. The consistency of the effect in men and women and the coupling of mortality to severity of retinopathy are especially significant (Figs. 2 and 3). This strengthens the inferences that retinopathy is, in fact, predictive of mortality and that microvascular and macrovascular diseases are not independent events (26). Why retinopathy is predictive of mortality requires further investigation. It is likely that the development of diabetic complications is indicative of a generalized worsening that leads to mortality. The processes that are worsening, though, are not understood. There appear to be at most moderate changes in traditional cardiovascular risk factors, but these in no way explain the overall increased mortality. Perhaps, as has been suggested (34), the metabolic events altered during the progression of diabetes serve to accelerate atherosclerotic advancement. Atherosclerotic initiation, however, may be under the control of more traditional factors (34). Understanding the mechanisms of such acceleration seem to be of highest priority. Until this understanding is reached, retinopathy is an accessible monitor for identifying individuals at substantial risk for premature mortality. In these individuals, aggressive action to interrupt or slow the natural history of diabetes is warranted. This is particularly true among high-risk groups such as Hispanics, in which diabetes already exacts a major toll, but this is only a portion of that to be realized as the population continues to grow and age.

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