Sex Differences in the Effect of Diabetes Duration on Coronary Heart Disease Mortality

Sundar Natarajan, MD, MSc; Youlian Liao, MD; Debajyoti Sinha, PhD; Guichan Cao, MS; Daniel L. McGee, PhD; Stuart R. Lipsitz, ScD

Background: It is not known whether the coronary heart disease (CHD) mortality risk associated with recent (RDM; <10 years) or long-standing diabetes mellitus (LDM; ≥10 years) varies by sex.

Methods: The relationship between diabetes duration and CHD mortality was evaluated among 10,871 adults (aged 35-74 years at baseline) using the 1971-1992 National Health and Nutrition Examination Survey Epidemiologic Follow-up Study.

Results: The CHD mortality rates per 1000 person-years in men with no myocardial infarction (MI) or diabetes, MI only, RDM only, LDM only, MI and RDM, and MI and LDM were 5.5 (95% confidence interval, 4.8-6.2), 15.2 (11.6-20.0), 13.2 (7.9-22.1), 11.4 (6.4-20.3), 36.0 (16.7-77.7), and 35.4 (14.0-89.7), respectively. The corresponding rates in women were 2.9 (2.5-3.3), 7.3 (5.0-10.8), 5.2 (3.5-7.7), 10.7 (7.5-15.5), 9.3 (4.3-19.9), and 21.6 (6.1-76.0), respectively. Compared with MI, the multivariate hazard ratios and their 95% confidence intervals (adjusted for age, race, smoking, hypertension, total cholesterol level, and body mass index) for fatal CHD in men with RDM, LDM, MI and RDM, and MI and LDM were 0.7 (0.3-1.3), 0.8 (0.4-1.4), 3.2 (1.4-7.4), and 2.4 (0.8-6.7), respectively. The corresponding ratios in women were 0.9 (0.6-1.3), 1.8 (1.1-3.2), 1.3 (0.5-3.5), and 1.6 (0.2-10.9), respectively.

Conclusions: In men, RDM and LDM were associated with as high a risk for CHD death as MI. In women, although RDM had a CHD mortality risk similar to MI, LDM had an even greater risk. Because women with LDM are at very high risk for CHD mortality, current guidelines may need to be further refined to match intensity of treatment to risk in these women.

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Coronary Heart Disease (CHD) is the leading cause of mortality and morbidity in developed countries, with a high case-fatality rate, emphasizing the need for aggressive preventive strategies. Recent data indicate that individuals with diabetes mellitus have as high a risk for fatal CHD as do individuals with established CHD.1 Previous studies have shown that diabetes has a greater impact on the risk for CHD in women than in men. In contrast to the substantial decrease in CHD mortality in individuals without diabetes, national trends demonstrate a modest decline in heart disease mortality in men with diabetes and an increase in heart disease mortality in women with diabetes.2 This emphasizes the need to further understand sex differences in the risk associated with diabetes.

Recent guidelines recommend aggressive management of other CHD risk factors in individuals with diabetes. Although diabetes has a greater effect on CHD mortality in women compared with men, it is not clear whether the risk associated with diabetes is constant or varies over time, and it is not known whether there is a differential risk over time by sex. To determine this for the US population as a whole, evaluation of a national population sample that includes men and women with diabetes is necessary. The specific aims of this investigation were: (1) to evaluate the independent effect of recent (RDM) and long-standing diabetes (LDM) on subsequent CHD mortality in men and women; (2) to quantify the sex-specific effects of diabetes duration on CHD mortality compared with prevalent myocardial infarction (MI), an accepted marker of increased CHD mortality risk; and (3) to determine the effect of each additional year of diabetes on CHD mortality.

**METHODS**

**STUDY DESIGN AND STUDY SAMPLE**

This analysis used cohort data from the First National Health and Nutrition Examination Survey (NHANES I) and the NHANES III Epidemiologic Follow-up Study (EFS). The NHANES I is a representative sample of the noninstitutionalized US civilian population, age 1 year and older, selected to be representative of the US population. The NHANES III EFS is a cohort study of 10,871 participants who participated in the initial NHANES III examination and who were followed up to become eligible for the NHANES I follow-up study. The NHANES III EFS includes participants from all age groups (1 year and older), but the focus of the current analysis is on adults aged 35-74 years at baseline. The analysis includes participants with and without diabetes mellitus at baseline and participants who were subsequently diagnosed with diabetes mellitus during the follow-up period. The study population was divided into three age groups: 35-44 years, 45-54 years, and 55-74 years. The primary exposure variables were diabetes duration (RDM and LDM) and diabetes status (with or without diabetes at baseline). The primary outcome variable was CHD mortality. The analysis included multivariate Cox proportional hazards regression models to estimate the hazard ratios and 95% confidence intervals for CHD mortality in men with RDM, LDM, MI and RDM, and MI and LDM. The models were adjusted for age, race, smoking, hypertension, total cholesterol level, and body mass index. The analysis was performed using the Statistical Analysis System (SAS) software, version 9.1.3.
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men</th>
<th>Women</th>
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<tbody>
<tr>
<td></td>
<td>Diabetes Only</td>
<td>No Diabetes</td>
</tr>
<tr>
<td>Participants, No. (%)</td>
<td>113 (2.0)</td>
<td>64 (1.1)</td>
</tr>
<tr>
<td>Age, mean (SE), y</td>
<td>58.2 (1.2)</td>
<td>59.2 (2.3)</td>
</tr>
<tr>
<td>BMI, mean (SE)</td>
<td>26.2 (0.9)</td>
<td>26.3 (0.6)</td>
</tr>
<tr>
<td>Current smokers, % (SE)</td>
<td>43.6 (8.2)</td>
<td>247 (7.5)</td>
</tr>
<tr>
<td>Total cholesterol level, mean (SE), mg/dL</td>
<td>229 (9.0)</td>
<td>231 (7.2)</td>
</tr>
<tr>
<td>Hypertension, % (SE)</td>
<td>58.4 (8.5)</td>
<td>69.1 (9.2)</td>
</tr>
<tr>
<td>White, % (SE)</td>
<td>89.2 (2.8)</td>
<td>810 (6.8)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); LDM, long-standing (>10 y) diabetes mellitus; MI, myocardial infarction; RDM, recent (<10 y) diabetes mellitus.

Because of rounding errors, some of the percentages may not total 100.

RESULTS

We initially performed analyses separately by sex. We compared baseline characteristics for a 6-level composite diabetes duration/MI variable that included no MI or diabetes, MI only, RDM only, LDM only, MI and RDM, and MI and LDM. Age-adjusted CHD mortality rates were obtained by a life-table product-limit method. Age-adjusted CHD mortality curves were determined for the 6-level diabetes duration–MI variable, and we tested the equality of curves by means of a Wald statistic.

We determined the independent effect of RDM or LDM on CHD mortality using Cox proportional hazards models. The proportionality assumption was tested and met. All multivariate analyses adjusted for baseline age, race, hypertension, smoking, serum total cholesterol level, and BMI, and the relative risks were reported as hazard ratios (HR). Because results of adjustment for menopause were not significant, adjustment for menopause was not included in the final models. Persons without diabetes or MI were initially used as the reference group. Then, to quantify the effect of RDM or LDM on CHD mortality, persons with prevalent MI were used as the comparison group. To formally test for sex differences in the effect of diabetes duration and MI on CHD mortality, interactions between sex and the 6-level composite diabetes duration–MI variable were tested in a hierarchical Cox model combining men and women. The effect of each additional year of diabetes was determined using diabetes duration as a linear variable in a Cox model that included baseline age, race, MI, hypertension, smoking, serum total cholesterol level, and BMI. All analyses were performed using SAS and SUDAAN and used the appropriate weighting and clustering variables to obtain population estimates.

Table 1 presents the baseline characteristics. In both men and women, there were fewer current smokers and more subjects with hypertension in the LDM groups. There were no significant differences in BMI or total cholesterol level between the RDM and LDM groups in men or in women. Women with LDM were older than women with RDM.

The age-adjusted CHD mortality rates per 1000 person-years (Table 2) in men with RDM only (13.2; 95% con-
CHD mortality curves for the different categories in men and women are shown in the Figure. There was no significant difference (P > .05) in age-adjusted 20-year CHD mortality rate among men with RDM alone (43%), LDM alone (56%), or MI alone (47%). In contrast, the 17-year mortality rate in women with LDM alone was significantly (P < .05) greater (51%) than the 20-year rates in women with RDM alone (22%) or MI alone (42%).

The independent risk for CHD mortality associated with RDM, LDM, or prevalent MI was determined from Cox models (Table 2). After multivariate adjustment, the relative risk for CHD death was similar in men with MI alone (HR, 3.4; 95% CI, 2.5-4.6) RDM (HR, 2.0; 95% CI, 1.0-4.0) or LDM (HR, 2.6; 95% CI, 1.5-4.7). In women, however, LDM was associated with a higher relative risk (HR, 4.8; 95% CI, 3.0-7.8) than RDM (HR, 1.5; 95% CI, 0.9-2.5) or MI (HR, 2.6; 95% CI, 1.6-4.3). To further quantify the risk associated with RDM or LDM, MI was used as the comparison group in the Cox model (Table 2). In men, RDM (HR, 0.7; 95% CI, 0.3-1.3) and LDM (HR, 0.8; 95% CI, 0.4-1.4) had a risk for CHD death equivalent to that of prevalent MI. In women, however, although RDM (HR, 0.9; 95% CI, 0.6-1.3) was associated with a risk for fatal CHD as high as that for MI, LDM (HR, 1.8; 95% CI, 1.1-3.2) had a greater risk for CHD mortality than did prevalent MI.

To formally test whether the relationship between diabetes duration and MI with CHD mortality depends on sex, interactions between sex and the composite diabetes duration–MI variable were tested with men and women combined. Significant interactions (P < .02) were found, implying that the effect of diabetes duration and MI on CHD mortality differs for men and women. The HRs from the model with interactions are presented in Table 3.
had an HR of 1.6, whereas women with LDM had an HR of 4.9. Women with LDM had a risk for CHD death similar to that of men with RDM or LDM; ie, LDM seems to remove the female protection against CHD.

To elucidate the effect of each year of diabetes on risk for fatal CHD, Cox models examined duration of diabetes (in years) as a continuous variable while adjusting for baseline age, smoking, total cholesterol level, BMI, hypertension, race, and prevalent MI. Each additional year of diabetes was associated with an HR of 1.07 (95% CI, 1.05-1.09) in men and 1.08 (95% CI, 1.06-1.10) in women.

**COMMENT**

This population-based analysis reemphasizes the magnitude of diabetes as a major risk factor for CHD mortality in men and women, documents sex differences in the effect of diabetes duration on CHD mortality risk, and quantifies it by comparing the risk with that in individuals with prevalent MI. In men, those with RDM and those with LDM had risks for CHD death equivalent to that for those with prevalent MI. In women, although those with RDM had a risk for CHD death as high as that for those with prevalent MI, LDM was associated with an even greater risk. Because women in the LDM group had a rate of CHD death as high as that of men with diabetes, LDM seems to remove the female protection against CHD death. Finally, each additional year of diabetes was associated with an increased risk for CHD death in both men and women.

Women, but not men, with LDM were older and had a larger proportion of persons with hypertension than did women with RDM. Even after adjusting for these and other risk factors in multivariate Cox models, LDM was associated with an increased risk for CHD mortality. Although sex differences among individuals with diabetes have been noted regarding triglyceride and high-density lipoprotein cholesterol levels, endothelial dysfunction, levels of lipid peroxidation, and nitric oxide production, little is known regarding the differential sex effects of diabetes duration. Long-standing diabetes may have greater deleterious effects on all these mechanisms. One previous study postulated that diabetes duration increases incident CHD by effects associated with longer duration of hyperglycemia such as longer exposure to a procoagulant state (eg, greater thrombosis risk, accelerated atherosclerosis) and increased arterial wall protein glycation leading to luminal occlusion.

Findings from the Rancho Bernardo Study indicate that women with diabetes have a poor survival rate after CHD and that this may be worse in women with diabetes of longer duration. Results of the Nurses’ Health Study, which included only women, indicated that the risk for fatal CHD increased monotonically with the duration of diabetes. They found that the relative risks (adjusted for age, BMI, smoking, menopausal status, and family history of premature MI) for fatal CHD in those with diabetes for 11 to 15, 16 to 25, and more than 25 years were 5.5, 6.4, and 11.9, respectively; the relative risk for fatal CHD in those with prevalent CHD in the same model adjusting for the same covariates was 5.5. Data from the Pittsburgh Epidemiology of Diabetes Complications Study, which included only patients with type 1 diabetes, as well as a study of elderly Finns with type 2 diabetes, showed an association between duration of diabetes and fatal cardiovascular events but did not evaluate sex differences. Our analysis evaluated US population-based data with maximal follow-up of more than 20 years, included men and women belonging to different races, and adjusted for important confounders to provide insights regarding the differential effect of diabetes duration in men and women. Because diabetes and MI have marked sex differences in subsequent CHD rates, it is crucial to analyze them by sex. Although previous studies have shown a greater impact of diabetes in women compared with men, they did not evaluate the effect of diabetes duration and did not determine the relative strength of the association by comparison with a marker of increased risk.

As expected, both in men and in women, persons with MI and diabetes had very high CHD mortality, and the patterns are consistent with that seen for the diabetes-only or MI-only groups. In women, the ranking of CHD mortality risk seems to be highest for LDM and MI, followed by LDM only, RDM and MI, and then RDM. In men, the ranking of CHD mortality risk seems to be highest for LDM and MI or RDM and MI, followed by MI and RDM, and then RDM. However, because of the small sample with diabetes and MI, which provides less power to detect differences particularly in studies using a complex sampling design, caution is needed when interpreting and comparing the risk associated with the combined diabetes-MI groups.

The results of this investigation should be interpreted while taking into account certain limitations. First, information regarding family history of CHD, high-
density lipoprotein cholesterol level, renal function, type of diabetes treatment, diabetes-related comorbidities, depression, and newer vascular risk factors (levels of fibrinogen, homocysteine, and C-reactive protein) was not available. Therefore, we were unable to adjust for these confounders. Second, information on prevalent MI and diabetes was obtained by self-report, which may have underestimated them because of lack of awareness and the use of less sensitive criteria for diagnosis of diabetes and MI during the time of the baseline examination. Previous studies have demonstrated the validity of self-report for these conditions and this did not differ by sex.25-27 Third, death certificate information is not completely accurate to classify cause of death, which may have biased our findings toward the null. Fourth, participants were followed up for a 20-year period, and these analyses have not accounted for temporal changes in diagnostic criteria and treatment for diabetes and MI. Fifth, because we did not have information on hormone therapy, we did not adjust for it in the analyses. We adjusted for menopause status, but because it was not significant, it was not included in the final model. Finally, it is very difficult to estimate duration of diabetes accurately.

Despite these limitations, this analysis provides new information regarding the effect of diabetes duration on CHD mortality by quantifying the dramatic impact of LDM in women after accounting for other known CHD risk factors. These findings support the need for intensive approaches to prevent CHD in persons with diabetes. Although improved glycemic control has not been definitively proven to decrease CHD events, the benefits from aggressive treatment of hypertension, dyslipidemia, and platelet responsiveness are established.

Population-based analyses indicate that diabetes prevalence is likely to double in the early 21st century, with a corresponding increase in diabetes-related illness burden.28 Because treating dyslipidemia in diabetic persons without cardiovascular disease may be as cost-effective as treating nondiabetic persons with cardiovascular disease,29 and because women with LDM are at higher risk (based on our data), it is likely that treating them will be even more cost-effective. Because the intensity of cardiovascular preventive measures in diabetes is based on their cardiovascular risk, and because women with LDM may be at higher risk than women with established MI, current guidelines for treating women with LDM may need to be further refined.

This US population-based prospective study demonstrates that the effect of diabetes duration on CHD mortality varies by sex. In men, those with RDM or LDM have a risk for CHD mortality as high as that for men with MI. In women, although those with RDM have a risk for CHD death that is equivalent to that for women with prevalent MI, those with LDM have an even greater risk. Therefore, current cardiovascular prevention recommendations in women may need to be further refined to match intensity of treatment to CHD mortality risk. This analysis should provide the impetus to further improve current diabetes-associated CHD risk assessment to decrease the very high risk for CHD death associated with diabetes.

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Correspondence: Sundar Natarajan, MD, MSc, 423 E 23rd St, Room 11101-S, New York, NY 10010 (sundar.natarajan@med.nyu.edu).

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Additional Information: We obtained public-use NHANES I Epidemiologic Follow-up Study data from the National Center for Health Statistics.

CONCLUSIONS

REFERENCES