Dyslipidemia and Ischemic Heart Disease  
Mortality Among Men and Women With Diabetes

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Background  We investigated whether the greater increased risk of ischemic heart disease mortality associated with diabetes among women compared with men could be explained by their more pronounced lipoprotein abnormalities.

Methods and Results  Seventy-six men and 45 women with diabetes and 327 men and 496 women without diabetes were followed for an average of 16 years in a population-based study. Cox proportional hazards models were used to determine the relative hazard of ischemic heart disease mortality for changes in lipoprotein subfractions after adjustment for age, hypertension, obesity, smoking, exercise, alcohol consumption, and estrogen use (among women). The relative hazard of ischemic heart disease mortality among diabetic women was 1.76 (P=.10) for a 10-mg/dL decrement in high-density lipoprotein cholesterol (HDL-C) and 3.13 (P=.01) for a 1-U increment in log, very-low-density lipoprotein cholesterol (VLDL-C). The risk of ischemic heart disease mortality among diabetic women relative to nondiabetic women for an HDL-C level of 50 mg/dL and a log, VLDL-C of 3 (about 20 mg/dL) were 4.1 and 3.4, respectively (P<.05). These lipoprotein changes were not associated with ischemic heart disease mortality among men or among nondiabetic women.

Conclusions  Excess ischemic heart disease mortality among diabetic women is partially explained by deleterious levels of HDL-C and VLDL-C. HDL-C levels of ≤50 mg/dL and VLDL-C levels of ≥20 mg/dL appear to predict ischemic heart disease mortality among these women and may help identify women who would benefit most from intervention. (Circulation. 1994;90:991-997.)

Key Words  • ischemia • mortality • diabetes mellitus • lipoproteins

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In western societies, women enjoy an advantage relative to men with regard to death from ischemic heart disease.1 In the face of diabetes, however, women lose this favored status and have rates of ischemic heart disease (IHD) mortality that approach those of men.2 The reason for this difference remains uncertain, but it persists after adjustment for major risk factors, including smoking, hypertension, and hypercholesterolemia.3 In the general population, high-density lipoprotein cholesterol (HDL-C) levels are higher in women than in men. Low HDL-C has been associated with IHD mortality in both sexes, and it has been suggested that HDL-C may be a more important protective factor for IHD in women.4-12 Adults with non-insulin-dependent diabetes (NIDDM) have been reported to have lower HDL-C levels and higher very-low-density lipoprotein cholesterol (VLDL-C) levels than those without diabetes, and this differential is greater in women.13,14 This low HDL-C, high VLDL-C pattern is the characteristic dyslipidemia of diabetes. In contrast, LDL-C levels among persons with and without diabetes do not differ significantly.15,16

Whether decreases in HDL-C or increases in VLDL-C among women with diabetes could account for their loss of IHD survival advantage has not been reported previously. In this study, we examine the contribution of dyslipidemia to the sex difference in IHD mortality risk associated with diabetes.

Methods

Between 1972 and 1974, 82% of adults >30 years old in a predominantly white, upper-middle-class community in southern California participated in a heart disease risk factor survey. At that time, height, weight, blood pressure, fasting total plasma cholesterol, fasting triglycerides, and fasting plasma glucose (FPG) were measured, and a history of diabetes and cigarette smoking was obtained. Previous reports describe the characteristics of this population and the prevalence of diabetes.17,18 Within 100 days of the first visit, one third of this cohort was invited to participate in a more extensive evaluation that included the measurement of lipoproteins. This sample was constructed of a 15% random sample of the initial cohort selected independently of previously measured lipid levels and an age- and sex-specific hyperlipidemic sample defined as those in the upper 10% in cholesterol, the upper 5% in triglycerides, or those who reported using lipid-lowering drugs. Ninety-two percent agreed to participate.

Medical and behavioral characteristics were determined by trained interviewers by means of a structured questionnaire. Subjects were asked about current cigarette smoking, number and type of alcoholic beverages consumed in the past week, and vigorous physical activity at least three times per week.
Height and weight were measured with participants in light clothing and without shoes, and obesity was assessed by body mass index (weight in kilograms divided by height in meters squared). Blood was obtained by venipuncture between 7 and 11 AM after a minimum 12-hour fast. FPG was measured by a hexokinase method. Lipids and lipoproteins were measured in a Lipid Research Clinic laboratory according to the procedures outlined in the Lipid Research Clinic's "Manual of Laboratory Operations." In brief, lipoprotein cholesterol levels were obtained by separating the plasma into lipoprotein fractions by a combination of preparative ultracentrifugation and precipitation with heparin and manganese chloride. These procedures yielded a direct estimate of HDL-C and indirect estimates of low-density lipoprotein cholesterol (LDL-C) and VLDL-C. Precipitated samples that failed to sediment because of elevated triglyceride levels were centrifuged without density adjustment, floating triglyceride-rich lipoproteins were removed, and the infranatant fraction was treated with manganese to remove LDL-C.

The vital status of >99% of the cohort was determined annually to 1990, an average of 16 years of follow-up. Death certificates were obtained for all decedents and coded for cause of death by a certified nosologist using the ninth revision of the "International Classification of Diseases, Adapted" (ICDA-9). IHD mortality (ICDA-9 codes 410.0 through 414.0) was used as the end-point criterion. For the first 10 years of this study, validation of death certificates was performed whenever cardiovascular disease appeared anywhere on the death certificate. Information was obtained from next of kin, physicians, and/or hospital records. Based on review by a panel of cardiologists, the predictive value of the nosologist classification was 86% for IHD mortality. Validation of death certificates has continued on a subsample of the population to the present, and the predictive value has never fallen below 85%.

For this analysis, subjects were classified as having diabetes, defined by personal history, FPG levels ≥140 mg/dL (7.7 mmol/L), and/or use of diabetes medications; or as not having diabetes, defined as FPG levels <110 mg/dL (6.1 mmol/L). Personal history of diabetes was validated in 85% of cases. Persons with indeterminate FPG levels (110 to 139 mg/dL or 6.1 to 7.6 mmol/L) were excluded from analysis to reduce misclassification bias. All diabetic and nondiabetic subjects ≥30 years old who were fasting at least 12 hours and who were not pregnant were included in the analysis. All participants gave written informed consent. The study was approved by the University of California Institutional Review Committee.

The distributions of age-adjusted covariates for diabetic and nondiabetic men and women were computed by ANCOVA for continuous variables and by the direct method for categorical variables. VLDL-C levels were first logarithmically transformed to correct for skewness in their distributions. HDL-C and LDL-C levels were sufficiently normally distributed that logarithmic transformation was not required. Boxplots were used to examine the distributions of lipoproteins by sex, diabetes, and IHD mortality status. The upper and lower poles of the boxes represent the first and third quartiles of the lipoprotein distribution; the "whiskers" and points extending vertically from the boxes show the minimum and maximum levels; and the cross and bar within each box represent the mean and median values, respectively (Figs 1 and 2). Cox regression models were used to determine the effect of sex and other covariates on cumulative IHD mortality in the cohort. Sex-specific Cox regression models were used to determine
potential interactions of HDL-C, VLDL-C, and the ratio of HDL-C to VLDL-C with other covariates on the risk of IHD mortality. Differences between men and women were tested in models with both sexes combined, adjusted for age and other covariates. Differences between groups were considered significant at $P=.05$, and interactions were considered important at $P=.15$. All $P$ values are for two-tailed tests. Statistical Analysis System (SAS) was used for all analyses.24

### Results

During the baseline survey, 76 diabetic and 327 nondiabetic men and 45 diabetic and 496 nondiabetic women were identified. Fifty-seven percent of the men and 58% of the women with diabetes were classified as having diabetes on the basis of personal history. Among men and women with diabetes, the proportion using any diabetes medication was similar: 30% and 24%, respectively. Among nondiabetic men and women, there were 101 and 112 deaths, respectively, of which 35 and 23, respectively, were attributed to IHD. Among diabetic men and women, there were 32 and 23 deaths, respectively, of which 12 and 8, respectively, were attributed to IHD. The age-adjusted relative hazard (RH) of IHD mortality in diabetic versus nondiabetic subjects was 1.53 in men and 3.59 in women.

Table 1 shows the mean ages and the age-adjusted means of blood pressure and lipoprotein levels by sex and diabetes status. Both men and women with diabetes were older and had higher log, VLDL-C levels than those without diabetes. The women with diabetes had higher systolic and diastolic blood pressures than women without diabetes and tended to have lower HDL-C levels ($P=.06$). Men with diabetes had significantly lower HDL-C and LDL-C levels than men without diabetes. In general, lifestyle factors known to confound HDL-C did not differ by diabetes status (Table 2). Women with diabetes, however, were less likely to use estrogens ($P<.05$) and more likely to report current smoking ($P=.07$) than nondiabetic women. Because the LDL-C levels were not significantly higher among diabetic subjects, the remainder of the analyses focused on their less favorable HDL-C and VLDL-C levels.

Figs 1 and 2 use boxplots to display the range of unadjusted HDL-C and log, VLDL-C levels for men and women by diabetes and IHD mortality status. Among men with and without diabetes and among women without diabetes, there was no association between mean HDL-C and IHD mortality. In contrast, among women with diabetes, mean HDL-C levels were significantly lower among the women with fatal IHD. It is also noteworthy that the diabetic women with fatal IHD had HDL-C levels comparable to those of men. Similarly, among both groups of men and among women without diabetes, there was no association between

| TABLE 1. Distribution of Age and Age-Adjusted Blood Pressure and Lipoprotein Levels Among Men and Women by Diabetes Status; Rancho Bernardo, Calif, 1972 Through 1975 |
|-------------------|-------------------|-------------------|-------------------|-------------------|
|                   | Nondiabetic (n=327) | Diabetic (n=76)   | Nondiabetic (n=496) | Diabetic (n=45)   |
|                   | Mean  | SEM  | Mean  | SEM  | Mean  | SEM  | Mean  | SEM  |
| Age, y            |       |      |       |      |       |      |       |      |
| 57.2              | 14.5  | (SD) | 61.7  | 12.0† | 57.6  | 13.8 | 61.0  | 11.6† |
| SBP, mm Hg        | 153.5 | 1.0  | 156.2 | 2.1  | 149.0 | 0.8  | 160.5 | 2.8† |
| BP, mm Hg         | 102.1 | 0.5  | 101.5 | 1.1  | 98.3  | 0.4  | 102.7 | 1.5† |
| HDL-C, mg/dL      | 49.9  | 1.0  | 45.4  | 2.0† | 66.1  | 0.8  | 61.0  | 2.6* |
| log, VLDL-C, mg/dL| 2.6   | 0.6  | 3.1   | 0.1† | 2.2   | 0.1  | 2.9   | 0.2† |
| LDL-C, mg/dL      | 157.0 | 2.2  | 145.8 | 4.6† | 158.3 | 1.8  | 159.4 | 6.0  |

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol. Values expressed in mg/dL can be converted to mmol/L by multiplying by 0.02586.

* $P<.10$, † $P<.05$, ‡ $P<.01$ for diabetics vs nondiabetics of given sex.

| TABLE 2. Percent Distribution of Age-Adjusted Lifestyle Factors Associated With HDL-C Among Men and Women by Diabetes Status; Rancho Bernardo, Calif, 1972 Through 1975 |
|-------------------|-------------------|-------------------|-------------------|-------------------|
|                   | Men               | Women             |
|                   | Nondiabetic       | Diabetic          | Nondiabetic       | Diabetic          |
| BMI ≥26.5         | 39.7              | 41.5              | 19.5              | 30.4              |
| Current smokers   | 19.9              | 13.9              | 24.3              | 35.7*             |
| Exercise (≥3 times/wk) | 15.8              | 6.8               | 7.3               | 7.3               |
| Alcohol (≥2 drinks/d) | 30.8              | 31.4              | 17.2              | 12.7              |
| Using estrogens   | . . .             | . . .             | 34.8              | 18.6†             |

HDL-C indicates high-density lipoprotein cholesterol; BMI, body mass index (weight in kilograms divided by height in meters squared).

* $P<.10$, † $P<.05$ for diabetics vs nondiabetics of given sex.
The models were used to determine the RH of IHD mortality for diabetic and nondiabetic subjects for a 10-mg/dL (0.26-mmol/L) decrement in HDL-C, which approximated 1 SD for HDL-C in this cohort. In the age-adjusted model for men, the corresponding RH was 1.00 for diabetic subjects and 1.09 for nondiabetic subjects, indicating that decreasing HDL-C did not contribute to IHD mortality in men. Conversely, in the age-adjusted model for women, the RH was 1.88 for diabetic subjects ($P=.06$) and 1.06 for nondiabetic subjects ($P=.65$), suggesting that decreasing HDL-C predicted IHD mortality in diabetic but not nondiabetic women; this difference between diabetic and nondiabetic women was statistically significant ($P=.12$). The addition of other covariates known to confound HDL-C (high body mass index, high blood pressure, exercise, consumption of alcoholic beverages, and estrogen use in women) to the models did not substantially alter these results (Table 3). This suggests that the HDL-C effect observed in the diabetic women was independent of lifestyle factors that confound HDL-C.

To obtain meaningful RHs of IHD mortality among diabetic men and women, the RH of IHD mortality for five clinically relevant HDL-C levels (40, 50, 60, 70, and 80 mg/dL) were calculated. Table 4 shows the results of these sex-specific models. In the fully adjusted HDL-C model specific for men, the RH of IHD mortality in diabetic compared with nondiabetic subjects increased only modestly as HDL-C levels decreased (from 1.3 at HDL-C of 80 mg/dL to 1.8 at HDL-C of 40 mg/dL). Among women, however, the RH of IHD mortality in diabetic versus nondiabetic subjects increased dramatically as HDL-C decreased (from 0.9 at HDL-C of 80 mg/dL to 7.0 at HDL-C of 40 mg/dL). This effect reached statistical significance for HDL-C levels of ≤50 mg/dL, suggesting that diabetic women with low HDL-C levels are especially vulnerable to IHD mortality.

To examine the contribution of VLDL-C to IHD mortality, sex-specific age-adjusted Cox models were developed with diabetes, VLDL-C, and diabetes-VLDL-C interaction terms. The models were used to determine the RH of IHD mortality for diabetic and nondiabetic subjects for an increment of 1.0 in log VLDL-C, which approximated 1 SD for log VLDL-C in this cohort. In the age-adjusted model for men, the corresponding RH was 1.16 for diabetic subjects ($P=.55$) and 0.87 for nondiabetic subjects ($P=.31$),...
indicating that increasing VLDL-C did not contribute to IHD mortality in men. In the age-adjusted model for women, the RH was 3.31 in diabetic subjects (P = 0.02) and 0.83 in nondiabetic subjects (P = 0.38), suggesting that increasing VLDL-C had a substantial effect on IHD mortality in diabetic but not nondiabetic women; this difference was statistically significant (P = 0.016). This effect persisted after addition of other covariates to the models (Table 3).

As with the HDL-C models, the RH of IHD mortality among diabetic men and women at increasing levels of log VLDL-C was calculated. In the fully adjusted VLDL-C model specific for men, the RH of IHD mortality in diabetic compared with nondiabetic subjects increased modestly as VLDL-C levels increased (from 1.0 at log, VLDL-C of 1 to 3.2 at log, VLDL-C of 5). Among women, however, the RH of IHD mortality in diabetic versus nondiabetic subjects increased dramatically as log, VLDL-C increased (from 0.3 at log, VLDL-C of 1 to 45.3 at log, VLDL-C of 5). This suggests that diabetic women with high VLDL-C levels are at especially high risk for IHD mortality. Similar to the findings with HDL-C, this effect reached statistical significance for log, VLDL-C values of ≥3, suggesting that diabetic women with high log, VLDL-C values are at especially high risk for IHD mortality.

Discussion

Women with diabetes have been found to sustain higher rates of IHD than women without diabetes, but this finding has never been fully explained. Data from this study show that lower HDL-C levels and higher VLDL-C levels contribute substantially to the excess IHD mortality observed in this group.

About 40% of diabetes cases in this study were previously unrecognized and were defined by a single FPG of ≥140 mg/dL (7.7 mmol/L). Accepted diagnostic criteria for diabetes require at least two FPG’s >140 mg/dL. However, FPG is subject to less intraindividual variation than glucose challenge and, as defined here, is highly correlated with postchallenge hyperglycemia.25 Nevertheless, any misclassification of diabetes in this cohort should have been equally distributed among men and women and is not likely to have caused the observed sex differences. Misclassification of subjects as nondiabetic was minimized by defining normal glucose as an FPG <110 mg/dL (6.1 mmol/L) and should have served to accentuate outcome differences between diabetic and nondiabetic subjects.26

Misclassification of IHD was addressed through rigorous death certificate validation. Limiting cases to those with IHD listed as cause of death should have reduced misclassification as well.

Lipoproteins were measured in a Lipid Research Clinics laboratory. HDL-C is not subject to substantial intraindividual variability, and in this cohort, its levels generally varied in the direction expected when adjusted for confounders. HDL-C and VLDL-C levels vary depending on type of diabetes, diabetes treatment, and diabetes control, with lower HDL-C and higher VLDL-C levels generally reported among individuals with NIDDM.27 In this cohort, only one woman and seven men with diabetes were receiving insulin, and as described, a substantial proportion of cases were previously unrecognized. It can thus be posited that the majority of diabetes cases in this cohort were NIDDM, with lipoprotein alterations consequent to that.

About half of this cohort was selected for hyperlipidemia. Diabetes status was not a factor in selection, however, and except for lower HDL-C levels in diabetic men in the hyperlipidemic group, lipid and lipoprotein levels among diabetic subjects in the hyperlipidemic and random samples did not differ significantly. As expected, the hyperlipidemic sample contained a greater number of diabetic subjects, but the proportion with diabetes was increased similarly for both sexes. Only 3 men and 10 women in the cohort were using lipid-
lowering medications at baseline, and only one of these individuals, a man, had diabetes.

Previous studies have shown that diabetes imposes a greater risk of heart disease in women than in men and that this risk is not explained after adjustment for smoking, hypertension, and hypercholesterolemia. In the Framingham study, diabetes remained as a risk factor for IHD mortality in women, even after adjustment for HDL-C. In a recent study from Finland, low HDL-C and high VLDL-C contributed to IHD events in a population of subjects with NIDDM. In this study, we have examined the contribution of HDL-C and VLDL-C to IHD mortality among men and women with and without diabetes. Diabetic subjects in this cohort generally had the less favorable heart disease risk factor profiles expected, including lower levels of HDL-C and higher levels of VLDL-C. Despite the small number of subjects with diabetes and fatal IHD, the data suggest a strong association between these lipoprotein changes and IHD mortality among women with diabetes. That HDL-C and VLDL-C appear to be associated is not surprising, since VLDL-C production and HDL-C catabolism are so closely linked. The diabetic women without fatal IHD and the nondiabetic women had significantly higher HDL-C levels and significantly lower VLDL-C levels than the diabetic women with fatal IHD. This effect persisted after adjustment for lifestyle factors known to affect HDL-C and raises the possibility that diabetic women with high and low HDL-C levels may represent distinct subgroups. Those with lower HDL-C and higher VLDL-C levels may have genetically determined metabolic differences that predispose them to macrovascular complications.

Diabetic dyslipidemia has been characterized by increased levels and altered composition of VLDL-C and reduced levels and altered composition of HDL-C. Elevations of VLDL-C have been described among persons with NIDDM and have been reported to be more pronounced among women with diabetes. Reduced concentrations of HDL-C among persons with NIDDM have been attributed to both decreased lipolytic clearance of VLDL-C and to elevated hepatic lipase activity, which is thought to result in increased HDL-C catabolism. Altered enzymatic metabolism of HDL-C among diabetic subjects with low HDL-C has been reported, and this alteration is not explained by insulin treatment, endogenous insulin production, or degree of hyperglycemia. The lipoprotein measurements available in our data do not represent the full spectrum of lipoprotein composition and can only serve as markers for more subtle lipoprotein abnormalities. There is evidence, however, that reductions in HDL-C and increments in VLDL-C are proportionately greater among women with diabetes than men and that these lipoproteins are different among diabetic compared with nondiabetic individuals.

In this study, high VLDL-C levels and low HDL-C levels partially explain the excess RH of IHD mortality among women with diabetes. Other factors certainly contribute, but evidence that other factors differ by sex is lacking. That these lipoprotein disturbances do differ by sex strengthens the argument that they are likely to be explanatory in the excess IHD mortality among women with diabetes relative to women without diabetes.

From these data, we cannot address whether the changes in VLDL-C and HDL-C are merely markers for other unrecognized metabolic disturbances. For example, insulin resistance in NIDDM has been shown to be negatively correlated with HDL-C and positively correlated with VLDL-C, and hyperinsulinemia has been shown to be a risk factor for cardiovascular disease in women with hypertension, high VLDL-C, and low HDL-C. Whatever the mechanism, women with diabetes are more vulnerable to IHD mortality. This increased vulnerability is at least partly explained by altered lipoprotein levels. It is reasonable to conclude that, for women, the combination of diabetes, low levels of HDL-C, and high levels of VLDL-C constitutes a high-risk metabolic profile. These women merit intensive intervention to ameliorate their risk through exercise, avoidance of smoking, weight loss, and other lifestyle changes that improve lipid and lipoprotein profiles. Pharmacological interventions to elevate HDL-C have not been undertaken in women, but this high-risk group should be considered for inclusion when such studies are undertaken.

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