The Association of Comorbid Depression With Mortality in Patients With Type 2 Diabetes

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OBJECTIVE — We assessed whether patients with comorbid minor and major depression and type 2 diabetes had a higher mortality rate over a 3-year period compared with patients with diabetes alone.

RESEARCH DESIGN AND METHODS — In a large health maintenance organization (HMO), 4,154 patients with type 2 diabetes were surveyed and followed for up to 3 years. Patients initially filled out a written questionnaire, and HMO-automated diagnostic, laboratory, and pharmacy data and Washington State mortality data were collected to assess diabetes complications and deaths. Cox proportional hazards regression models were used to calculate adjusted hazard ratios of death for each group compared with the reference group.

RESULTS — There were 275 (8.3%) deaths in 3,303 patients without depression compared with 48 (13.6%) deaths in 354 patients with minor depression and 59 (11.9%) deaths among 497 patients with major depression. A proportional hazards model with adjustment for age, sex, race/ethnicity, and educational attainment found that compared with the nondepressed group, minor depression was associated with a 1.67-fold increase in mortality ($P = 0.003$), and major depression was associated with a 2.30-fold increase ($P < 0.0001$). In a second model that controlled for multiple potential mediators, both minor and major depression remained significant predictors of mortality.

CONCLUSIONS — Among patients with diabetes, both minor and major depression are strongly associated with increased mortality. Further research will be necessary to disentangle causal relationships among depression, behavioral risk factors (adherence to medical regimens), diabetes complications, and mortality.

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Patients with type 2 diabetes have a high prevalence of affective illness, with ~11–15% meeting the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for major depression (1). Major depression has been found to be a chronic or recurrent illness in most patients with type 2 diabetes (2). As many as two-thirds of patients with diabetes and major depression have been ill with depression for ≥2 years (2). Over a 5-year period, ~80% of patients with major depression and diabetes were found to have had one or more relapses (3).

Compared with patients with diabetes alone, patients with depression and diabetes have been shown to have poorer self-management (i.e., following diet, exercise regimens, and checking blood glucose) (4,5) and to have significantly more lapses in refilling oral hypoglycemic, lipid-lowering, and antihypertensive medications (4). Depressed patients with diabetes are also significantly more likely to have three or more cardiac risk factors (i.e., smoking, obesity, sedentary lifestyle, HbA_{1c} [AIC] >8.0%) compared with those with diabetes alone (6).

A meta-analysis of 27 cross-sectional studies showed that patients with depression and diabetes were significantly more likely to have macrovascular and microvascular complications (7). This association between complications and depression is likely to be bidirectional (8). Depression may increase the risk of complications because of the higher risks associated with poor self-care and adverse health behaviors (4–8) and because of neuroendocrine (9) and autonomic nervous system (10) abnormalities associated with depression. Depression can also be caused by complications due to either psychological reactions to changes in function (8) or aversive physical symptoms (such as chronic pain from neuropathy) (11) associated with complications.

Three recent longitudinal studies of community respondents have shown that comorbid depression is associated with higher mortality rates in patients with diabetes compared with patients with diabetes alone (12–14). Limitations of these studies included that all medical diagnoses were based on self-report data, no laboratory tests such as A1C levels were available, and the studies were based on relatively small numbers of patients with diabetes.

The Pathways Study (15) is a population-based epidemiologic study that successfully surveyed ~4,800 patients with diabetes enrolled in a health maintenance organization (HMO). This report examined the association of comorbid major or minor depression in patients with type 2 diabetes with mortality over a 3-year period. This study adds to the evidence from prior research because of the ability to link self-report and mortality data with

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Abbreviations: CAD, coronary artery disease; GHC, Group Health Cooperative; HMO, health maintenance organization.

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

medical data including physician diagnosis and laboratory testing (A1C).

RESEARCH DESIGN AND METHODS

— The Pathways Epidemiologic Study was developed by a multidisciplinary team from the Department of Psychiatry and Behavioral Sciences at the University of Washington and the Center for Health Studies at Group Health Cooperative (GHC). GHC is a nonprofit staff model HMO with 30 primary care clinics in western Washington State. The study protocol was reviewed and approved by institutional review boards at GHC and the University of Washington.

Study setting

Nine GHC clinics in western Washington were selected for the study based on three criteria: *1*) clinics with the largest number of patients with diabetes, *2*) clinics within a 40-mile geographic radius of Seattle, and *3*) clinics with the most racial and ethnic diversity.

Sample recruitment

Potential participants were sampled from adults in the GHC diabetes registry from the nine primary care clinics. Patients are added to the diabetes registry based on *1*) currently taking any diabetes medication, *2*) a fasting glucose ≥126 mg/dl confirmed by a second out-of-range test within 1 year, *3*) a random plasma glucose ≥200 mg/dl also confirmed by a second out-of-range test within 1 year, or *4*) a hospital discharge diagnosis of diabetes at any time during GHC enrollment or two outpatient diagnoses (ICD-9) of diabetes.

Patients were surveyed by mail in sequential waves, with ~700 questionnaires sent per month (2). A $3 gift card from a local store was included to encourage response. The invitation letter and survey booklet included all components of informed consent as well as a separate, specific consent for review of medical records. Those who did not respond but who did not refuse participation were mailed a second survey 4 weeks later, and a third attempt (including a telephone reminder) was made 6 months later.

Survey measures

The mail survey included questions regarding sociodemographic characteristics (age, sex, race, educational attainment, and marital status), diabetes characteristics (age at onset, initial treatment prescribed, and type and duration of treatment), and symptoms of depression (see below). Participants were classified as having type 1 diabetes if they developed their disease before age 30 years, insulin was the first treatment prescribed, and insulin was a current treatment. Patients with type 1 diabetes were excluded from the analysis.

The Patient Health Questionnaire-9 (16–18) was used to screen for depression. This questionnaire provides both a dichotomous diagnosis of major or minor depression and a continuous severity score. The Patient Health Questionnaire-9 diagnosis of major depression has been found to have high sensitivity (73%) and specificity (98%) for the diagnosis of major depression by structured interview (16,17). The criteria for major depression required the patient to have at least 2 weeks of five or more symptoms present for more than half the days, with at least one of these symptoms being depressed mood or anhedonia. The criteria for minor depression required the patient to have two to four depressive symptoms for more than half the days for at least 2 weeks, with at least one of these symptoms being depressed mood or anhedonia.

A measure using automated diagnostic (ICD-9) and laboratory data was developed to code for seven types of diabetes complications (retinopathy, neuropathy, nephropathy, cerebrovascular, cardiovascular, peripheral vascular, and metabolic) (18). This diabetes complication measure is similar to a previously developed measure that was based on automated data using ICD-9 codes as well as clinical data and has been found to correlate with medical costs in several studies (18,19). The RxRisk (20), which is a pharmacy-based measure of medical comorbidity, was used to measure non–diabetes-related medical illness severity.

We will report all-cause mortality data from March 2001 at the start of recruitment through 31 May 2005. The first 21 months of mortality data are based on both GHC-automated health care records and Washington State mortality data (March 2001 to 31 December 2003), whereas the last 17 months (1 January 2004 to 31 May 2005) uses GHC data alone. In the first 2 years of the study, GHC data included 90% of all deaths reported in the Washington State mortality data. Time of death was censored at the end of the study (31 May 2005), or the time of disenrollment, if disenrollment occurred between 31 December 2003 and 31 May 2005.

Statistical methods

We used χ^2 tests to examine differences in categorical baseline demographic and clinical characteristics across the three baseline depression groups (none, minor, and major) and ANOVA to test for overall group differences in continuous measures. We used a proportional hazards model to estimate the association of baseline characteristics with all-cause survival (21). Two multivariate models were developed, and our primary predictor was baseline depression status. The first model, which was our primary analysis, adjusted for confounding sociodemographic variables including sex, age, race/ethnicity (Caucasian, African American, Asian or Pacific Islander, and other), and education that were not likely to be mediators of the relationship between depression/diabetes and mortality. A second model adjusted for the variables in our primary model as well as behavioral and clinical variables that were likely to be mediators of the relationship between depression/diabetes and mortality including obesity (BMI >30 kg/m^2), smoking (yes/no), sedentary lifestyle (<1 day a week of exercise lasting ≥30 min), A1C ≥8%, diabetes treatment (diet only, any oral hypoglycemics, and any insulin use), RxRisk, and number of diabetes complications (none, one, and two or more). We checked the proportional hazards assumption by examining plots of the log [−log(survival)] versus log of survival time and using Schoenfeld residuals (22).

RESULTS

— Patients (n = 9,063) on the diabetes registry were mailed the study questionnaire. As described previously (2,4,6), 1,222 subjects were ineligible for the study. Of the remaining 7,841 eligible patients, 3,002 did not return the questionnaire. Of 4,839 who returned the questionnaire, 369 did not give permission to review medical records, 201 had type 1 diabetes, 54 were missing the education variable, 97 were missing race/ethnicity, and 7 had incomplete patient health questionnaires. The resulting study sample of 4,154 patients included 497 with major depression, 354 with minor depression, and 3,303 with no depression. For model 2, another 265 were missing at least one potential mediator: 63 were missing BMI, 68 were missing smoking status, 64 were missing exercise information, and 70 were missing A1C.

Table 1 describes demographic and clinical differences between three groups (none, minor, and major). There were sig-

Table 1—*Depression and demographic characteristics by depression grouping*

Variables	Total sample	No depression	Minor depression	Major depression	Overall test statistics χ^2 (df = 2)	Minor vs. none χ^2 (df = 1)	Major vs. none χ^2 (df = 1)	Major vs. minor χ^2 (df = 1)
n	4,154	3,303 (79.5)	354 (8.5)	497 (12.0)				
Female	2,023 (48.7)	1,555 (47.1)	178 (50.3)	290 (58.4)	<0.0001	0.2512	<0.0001	0.0197
High school or less	1,040 (25.0)	794 (24.0)	112 (31.6)	134 (27.0)	0.0056	0.0016	0.1380	0.1233
Unmarried and not living as married	1,396 (33.7)	1,061 (32.2)	128 (36.2)	207 (41.7)	0.0001	0.1282	<0.0001	0.1010
Employment (full or part time)	1,661 (41.1)	1,323 (41.0)	125 (36.8)	213 (45.0)	0.0920	0.1317	0.0953	0.0183
Race								
Caucasian	3,294 (79.3)	2,639 (79.9)	262 (74.0)	393 (79.1)	0.0021	0.0136	0.0072	
African American	350 (8.4)	265 (8.0)	35 (9.9)	50 (10.1)				0.1077
Asian	393 (9.5)	320 (9.7)	40 (11.3)	33 (6.6)				
Other	117 (2.8)	79 (2.4)	17 (4.8)	21 (4.2)				
Age (years)	64.2 ± 12.6	64.8 ± 12.3	64.7 ± 13.3	59.5 (13.0)	<0.0001	0.8580	<0.0001	<0.0001
RxRisk score					0.0083	0.0172	0.0409	
<1,300	798 (19.2)	628 (19.0)	74 (20.9)	96 (19.3)				
1,300 to 2,599	1,066 (25.7)	874 (26.5)	69 (19.5)	123 (24.8)				0.2637
2,600 to 4,399	1,122 (27.0)	910 (27.6)	96 (27.1)	116 (23.3)				
≥4,400	1,168 (28.1)	891 (27.0)	115 (32.5)	162 (32.6)				
Diabetes complications					<0.0001	0.0001	<0.0001	
<2	2,638 (63.5)	2,166 (65.6)	196 (55.4)	276 (55.5)				0.9617
≥2	1,516 (36.5)	1,137 (34.4)	158 (44.6)	221 (44.5)				
A1C level groups					<0.0001	0.2033	<0.0001	
<8.00%	2,607 (63.8)	2,129 (65.5)	216 (62.1)	262 (54.0)				0.0205
≥8.00%	1,477 (36.2)	1,122 (34.5)	132 (37.9)	223 (46.0)				
BMI	2,031 (49.6)	1,714 (52.6)	157 (45.1)	160 (32.7)	<0.0001	0.0076	<0.0001	0.0003
≤30.0 kg/m^2	2,062 (50.4)	1,542 (47.4)	191 (54.9)	329 (67.3)				
>30.0 kg/m^2								
Smoking currently	345 (8.4)	232 (7.1)	37 (10.6)	76 (15.6)	<0.0001	0.0182	<0.0001	0.0394
Treatment intensity								
None or diet	1,104 (26.6)	931 (28.2)	81 (22.9)	92 (18.5)	<0.0001	0.0011	<0.0001	0.0475
Oral hypoglycemic	1,924 (46.3)	1,567 (47.4)	156 (44.1)	201 (40.4)				
Insulin or insulin + oral hypoglycemic	1,126 (27.1)	805 (24.4)	117 (33.1)	204 (41.1)				
Exercise								
≤1 day per week	1,206 (29.5)	841 (25.9)	147 (42.0)	218 (44.7)	<0.0001	<0.0001	<0.0001	0.4417
2–7 days per week	2,886 (70.5)	2,413 (74.2)	203 (58.0)	270 (55.3)				

Data are means ± SD or *n* (%), unless otherwise indicated.

nificant differences on all demographic and clinical variables except employment status. Relative to patients with diabetes with no depression at baseline, patients with minor depression were less educated and less likely to be Caucasian, were more likely to have two or more diabetes complications and greater nondiabetes-related medical comorbidity, more likely to be treated with insulin and to have a BMI >30 kg/m^2, to be a current smoker, and to be sedentary. Relative to patients with diabetes with no depression at baseline, patients with major depression were significantly younger, less likely to be married, and more likely to be female, to have two or more diabetes complications and greater non–diabetes-related medical comorbidity, to be treated with insulin, to have an A1C ≥8.0% and BMI >30 kg/m^2, to be a current smoker, and to be sedentary. Compared with patients with minor depression, those with major depression were more likely to be female, unemployed, younger, to have an A1C ≥8.0%, BMI >30.0 kg/m^2, to be a current smoker, and to be treated with insulin.

Over a 3-year period, there were 275 (8.3%) deaths in 3,303 patients without depression compared with 48 (13.6%) deaths in 354 patients with minor depression and 59 (11.9%) deaths among 497 patients with major depression. Our primary analysis (controlling for sociodemographic confounders [Table 2]) shows that minor depression, major depression, older age, and male sex are associated with a significant increase in mortality over a 3-year period. Both minor and major depression remained significant predictors of mortality (Table 3) in analysis that also controlled for potential behavioral and disease severity mediators. Controlling for these mediators had little effect on the association of minor depres-

Table 2—*Proportional hazards model 1: using all deaths (both tapes and GHC, from 1 March 2001 through 31 May 2005)*

Variable	Estimate	SE	*P* value	Hazard ratio
Minor depression	0.51	0.157	0.002	1.67
Major depression	0.83	0.145	<0.0001	2.30
Male	0.19	0.104	0.06	1.21
Some college	−0.07	0.111	0.52	0.93
Age (years)	0.08	0.005	<0.0001	1.09
African American (versus white)	0.07	0.206	0.73	1.07
Asian (versus white)	−0.18	0.208	0.39	0.84
Other (versus white)	−0.12	0.414	0.77	0.88

sion with mortality (hazard ratio 1.67 vs. 1.46) but did decrease the effect of major depression on mortality (2.30 vs. 1.43). Older age, sedentary lifestyle, insulin use, and increased diabetes complications and non–diabetes-related medical comorbidity also were significant predictors of mortality.

CONCLUSIONS — Both major and minor depression were found to be associated with significantly higher mortality in patients with type 2 diabetes compared with nondepressed patients with diabetes alone. These data are similar to findings from several large epidemiologic studies that showed that patients with comorbid depression and diabetes compared with those with diabetes alone had a significantly higher mortality risk (12–14). Our findings extend the data from these two studies by including physician diagnoses of diabetes complications, automated pharmacy prescription data that help document other medical comorbidities, and laboratory testing (A1C values). We have shown that controlling for important potential behavioral and clinical mediators decreases the association of major depression with mortality to some degree but has little effect on the association of minor depression with medical comorbidity. These estimates may change more for patients with major compared with minor depression because the potential mediators were more strongly associated with major depression.

Sedentary lifestyle was a significant independent predictor of mortality in the fully adjusted model and has been shown to adversely affect mortality in patients with diabetes (13). Evidence suggests that depression and sedentary lifestyle are bidirectionally related; prior longitudinal studies have found that sedentary lifestyle predicts development of depression and depression predicts development of sedentary lifestyle (23). In our model that controlled for potential mediators, the effect of major depression may be reduced due to controlling for sedentary lifestyle. A recent randomized controlled trial that tested a depression quality improvement program in patients with diabetes and depression compared with usual primary care showed that improved outcomes of depression in intervention patients versus those treated in usual primary care were associated with significant increases in exercise and improved physical functioning over a 12-month period (24).

The increased mortality seen in patients with depression and diabetes compared with those with diabetes alone is similar to findings from a recent meta-analysis of the effect of depression on mortality in patients with coronary artery disease (CAD) (25). In 10 studies in patients with CAD, depression was associated with a 1.64 increased relative risk of mortality (25). These data in patients with CAD are important because diabetes has been recently labeled a cardiovascular illness (26). A total of 70–80% of patients with diabetes die from CAD, and patients with diabetes with no prior diagnosis of CAD have been found to have the same risk of myocardial infarction as nondiabetic patients with a prior history of myocardial infarction (26).

Depression may be associated with increased mortality in patients with diabetes because of both behavioral and biologic factors. Depression has been shown to be associated with poor adherence to self-care regimens in patients with diabetes (diet, exercise, and cessation of smoking) (4,5), poor adherence to all three categories of disease control medications (i.e., oral hypoglycemic, lipid-lowering, and antihypertensive) (4), and a twofold higher likelihood of having three or more of eight cardiac risk factors (6). Depression may also be associated with mortality due to poor glucose regulation (7,27) based on hypothalamic-pituitary axis abnormalities (9,27) as well as increased risk of myocardial infarction (12–14) and stroke (12–14) due to the association of depression with increased platelet adhesiveness and aggregation, increased markers of inflammatory response such as C-reactive protein levels, endothelial dysfunction, increased sympathoadrenal activity, and higher QT variability (9,10).

Limitations of this study include the fact that depression was measured at only one point in time. Chronicity of depression may be associated with even higher mortality rates. Adequate data on the cause of death were not available. The

Table 3—*Proportional hazards model 2: fully adjusted analyses*

Variable	Estimate	SE	*P* Value	Hazard ratio
Minor depression	0.38	0.161	0.019	1.46
Major depression	0.36	0.160	0.026	1.43
Male	0.11	0.110	0.329	1.11
Some colllege	−0.01	0.115	0.904	0.97
Age (years)	0.07	0.006	<0.0001	1.08
African American (versus white)	−0.06	0.220	0.798	0.94
Asian (versus white)	−0.07	0.220	0.745	0.93
Other (versus white)	−0.14	0.454	0.751	0.87
BMI >30 kg/m^2	−0.12	0.121	0.342	0.89
Current smoker	0.37	0.221	0.094	1.45
Sedentary lifestyle	0.34	0.112	0.003	1.40
A1C ≥8.0%	0.145	0.115	0.211	1.16
Use oral hypoglycemics (no insulin)	0.050	0.154	0.746	1.05
Any insulin use	0.465	0.164	0.005	1.59
RxRisk	0.067	0.008	<0.0001	1.07
One complication	−0.237	0.197	0.229	0.79
Two or more complications	0.580	0.170	0.001	1.79

study was completed in one geographic region of the country, limiting generalizability. Because >20% of our sample did not fill out the question on income, we did not include this variable in our models; however, educational level is a reasonable proxy for socioeconomic status.

In conclusion, in a population-based sample of patients with type 2 diabetes, both major depression and minor depression were associated with increased mortality rates over a 3-year period.

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