Published in final edited form as:

Gen Hosp Psychiatry. 2011 ; 33(5): 429–435. doi:10.1016/j.genhosppsy.2011.05.021.

Depression and Incident Diabetic Retinopathy: A Prospective Cohort Study

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Abstract

Objective—This study examined whether depression is associated with a higher incidence of diabetic retinopathy among adults with type 2 diabetes, after controlling for sociodemographic factors, health risk behaviors, and clinical characteristics.

Method—This study included 2,359 patients enrolled in Pathways Epidemiologic Follow-Up Study, a prospective cohort study investigating the impact of depression in primary care patients with type 2 diabetes. The predictor of interest was baseline severity of depressive symptoms assessed with the Patient Health Questionnaire-9 (PHQ-9). The outcome was incident diabetic retinopathy. Risk of diabetic retinopathy was assessed using logistic regression and time to incident diabetic retinopathy was examined using Cox proportional hazard models.

Results—Over a 5-year follow-up period, severity of depression was associated with an increased risk of incident retinopathy (OR = 1.026; 95% CI (1.002,1.051)) as well as time to incident retinopathy (HR = 1.025; 95% CI (1.009,1.041)). The risk of incident diabetic retinopathy was estimated to increase by up to 15% for every significant increase in depressive symptoms severity (five point increase on the PHQ-9 score).

Conclusion—Diabetic patients with comorbid depression have a significantly higher risk of developing diabetic retinopathy. Improving depression treatment in patients with diabetes could contribute to diabetic retinopathy prevention.

Keywords

depression; type 2 diabetes; diabetic retinopathy; microvascular complications; epidemiologic study

Introduction

Depression and diabetes mellitus are two of the most common diseases in the general population and often co-occur. A meta-analysis of 42 studies demonstrated that the

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prevalence of depression was twice as high among adults with diabetes compared to similar individuals without diabetes[1]. The relationship between depression and diabetes has been described as bidirectional. Depression is associated with a 40% to 60% increased risk of subsequent development of diabetes[2-6], and diabetes is predictor of future depressive episodes[2, 3, 7-9].

Comorbid depression and diabetes often result in increased disease burden (higher symptom severity[10, 11], lower adherence to treatment[11, 12], additive functional impairment [11, 13], decreased quality of life [14-18]) and higher mortality [19]. A meta-analysis of 27 studies found a significant association between depression and numerous diabetes complications (diabetic retinopathy, nephropathy, neuropathy, coronary artery disease, peripheral vascular disease and ischemic heart disease)[20]. These studies were all cross-sectional in design, thus, causality could not be determined. In a large scale prospective study investigating a population of elderly Mexican Americans with type 2 diabetes, Black concluded that comorbid depression at baseline was associated with an increased and earlier incidence of macrovascular and microvascular complications and mortality over a 7-year follow-up period[21]. Examining the same cohort of adults with type 2 diabetes from the present study, Lin found that depression was associated with a 25% increase of severe macrovascular complications and a 35% increase of severe microvascular complications. The composite microvascular complication measure included retinopathy, nephropathy, foot ulcers and amputations[22].

While several studies have examined the association between depression and microvascular and macrovascular complications, the literature on the relationship between depression and diabetic retinopathy is scarce. Diabetic retinopathy is one of the most frequent complications in patients with diabetes. In the United States, 40% of individuals with type 2 diabetes and 86% of individuals with type 1 diabetes will develop diabetic retinopathy[23]. It is considered the principal cause of impaired vision in patients between 25 and 74 years old, leading to 12, 000 to 24, 000 new cases of blindness each year[23, 24]. A few cross-sectional studies have shown an association between depression and retinal microvascular damage [25] or diabetic retinopathy in diabetic patients [26, 27] while other studies failed to do so[28, 29]. One prospective study of 66 children with type 1 diabetes identified depression as a risk factor for subsequent development of diabetic retinopathy[30]. In a longitudinal study of 581 African Americans adults with type 1 diabetes, Roy demonstrated a link between depression and incidence and progression of diabetic retinopathy[31, 32]. However, generalizability of these results is limited by the studies' relatively small samples and the specificity of the populations examined. Larger prospective studies investigating a more general population with type 2 diabetes are needed to better understand the relationship between depression and diabetic retinopathy.

The Pathways Study was a prospective population-based cohort study investigating the impact of depression in primary care patients with diabetes[33]. The current study proposes to utilize the Pathways Epidemiologic Follow-Up Study to assess the relationship between depression and subsequent risk of diabetic retinopathy over a 5-year period. We hypothesized that the presence of depression would be associated with a higher incidence of diabetic retinopathy among adults with type 2 diabetes.

Methods

Study Design - Pathways Epidemiologic Study

The Pathways Study was designed by a multidisciplinary team in the Department of Psychiatry and Behavioral Sciences at the University of Washington and the Group Health Research Institute. Group Health is an integrated health care system based on a mixed-

model prepaid health plan structure. It comprises 30 primary care clinics serving approximately 523,000 patients in western Washington State. The study protocol was reviewed and approved by institutional review boards at the University of Washington and at Group Health. The Pathways Study was a population-based cohort study that prospectively followed a population of patients with diabetes over a 5-year period.

Sample

The population studied was sampled between 2000 and 2002. The Group Health diabetes registry was used to identify adults who received care in one of nine primary care clinics in the Seattle and Puget Sound area. The clinics were selected because of their geographic location, the proportion of diabetic patients, and the socioeconomic, racial and ethnic diversity of the patient population they served.

Eligibility criteria included having any of the following in the 12 months preceding recruitment: prescriptions filled for insulin or oral hypoglycemic agents, two fasting plasma glucose levels > 126mg/dL, two random plasma glucose levels > 200mg/dL, two outpatient diagnoses of diabetes, or any inpatient diagnosis of diabetes.

A survey was sent by mail to patients identified from the registry to verify eligibility and to obtain consent to participate in the study. Five years after enrolling for the Pathways Study, all subjects were recontacted by mail or by telephone for the Pathways Epidemiologic Follow-Up Study. Subjects consenting for the Follow-Up Study were asked for permission to review electronic and paper medical records to collect information on medical conditions. For subjects deceased since the initial enrollment, the Group Health Institutional Review Board provided a waiver of consent to review electronic and paper medical records.

Subjects with a diagnosis of diabetic retinopathy prior to enrollment or who had no eye exam during the follow-up period were excluded. Those who had no eye exam in the 2 years prior to enrollment were also excluded (Figure 1).

Main Outcome

The outcome of interest was incident cases of diabetic retinopathy in the five years after the baseline questionnaire was returned. Automated data provided administrative and clinical information to identify patients with diabetic retinopathy, and the length of time between enrollment and the diagnosis. Patients with no evidence of diabetic retinopathy at baseline, who had retinal evaluations by an optometrist or an ophthalmologist and had ICD-9 codes 362.01 (background diabetic retinopathy, diabetic macular edema, diabetic retinal edema, diabetic retinal microaneurysms or diabetic retinopathy NOS) or 362.02 (proliferative diabetic retinopathy) during the follow-up period were included in the analyses as incident cases of diabetic retinopathy.

Predictor

The predictor of interest was baseline symptoms of depression. This was evaluated using the Patient Health Questionnaire-9 (PHQ-9)[34], a self-report measure of depressive symptom severity based on the Diagnostic and Statistical Manual of Mental Disorders - fourth edition. Each item is scored positive if endorsed as present more than half of the time or nearly all the time. We used the total score on the PHQ-9 as a continuous variable as the predictor measure. A significant change in the severity of depression is defined as a change of at least 5 points in the total score[35]. A PHQ-9 threshold of ≥ 10 for probable major depression has been shown to have moderate to high sensitivity (77-88%) and high specificity (88-94%) in relation to the diagnosis of major depression based on a structured psychiatric interview[35].

Potential Confounders

The potential cofounders for the association between depression and the incidence of diabetic retinopathy were selected a priori based on previous literature. Potential confounders identified from the mailed survey were sociodemographic characteristics (age, gender, race, educational attainment, marital status), clinical characteristics (height and weight, duration of diabetes, intensity of diabetes treatment - diet only, oral hypoglycemic only, or insulin, and enrollment status in Pathways Study [33]—intervention or control group) and health behaviors (smoking, physical activity, diet) which were obtained from the Summary of Diabetes Self-Care Questionnaire[36]. Automated clinical data provided information on non-diabetic medical comorbidities such as hypertension as well as glycemic control (HbA_{1C}). The severity of diabetic complications was measured using the Diabetes Complication Severity Index (DCSI), an automated data derived measure of diabetic complications based on ICD-9 diagnosis codes for diabetic complications and laboratory tests[37].

Statistical Methods

One-way analysis of variance (ANOVA) was used to assess univariate associations between continuous baseline sociodemographic and clinical variables and the baseline severity level of depression. We used χ^2 tests to examine the bivariate association between categorical baseline sociodemographic and clinical variables and the depression severity group.

Examining the relationship between depression and diabetic retinopathy, we used logistic regression as primary analysis and proportional hazards as a secondary measure. For the primary analysis, we first examined the association between baseline depression severity level and incident diabetic retinopathy, without adjustment. Then, four groups of potential confounding variables were successively added to the model. As depressed patients may be more likely to disenroll and also have been shown to have greater mortality[38], and therefore have a shorter period of observation, we first controlled for the number of days of follow-up. We then adjusted sequentially for sociodemographics variables (age, gender, race, education and marital status), baseline clinical characteristics (duration of diabetes, diabetes treatment, hypertension, diabetes complications and enrollment status in the Pathways randomized-controlled trial), and health behaviors (exercise, smoking, body mass index and HbA_{1C}).

We used Cox proportional hazards models to investigate the association between the depression severity score and the time to incident diabetic retinopathy. Subjects were censored at time of disenrollment, time of death or at the end of the study, whichever occurred first. We fit four proportional hazard models, introducing one additional group of covariates at each step. We used the same confounding variables groups as for the logistic regression models.

Analyses were performed with IBM SPSS Statistics 18 (SPSS Inc., Chicago, IL, USA) and STATA 11 (Stata Corporation, College Station, TX, USA) statistical software programs.

Results

Figure 1 illustrates the Pathways Epidemiologic and Follow-Up Study sample recruitment. For the Pathways Study, of the 9,064 subjects initially identified as eligible, 1,223 were non-eligible because of death, disenrollment, erroneous diagnosis of diabetes, or cognitive impairment. Of the 7,841 eligible subjects, 4,839 subjects returned the baseline questionnaire of which 216 were excluded because of a diagnosis of type 1 diabetes, resulting in a total cohort of 4,623 subjects with type 2 diabetes. For the Pathways Epidemiologic and Follow-up Study, 4,128 subjects consented for medical record review or

were under a waiver of consent from the institutional review boards. A total of 695 subjects had no retinal exam in the 2 years prior to enrollment, 843 already had a diagnosis of diabetic retinopathy and 231 had no retinal exam during the follow-up period. The final sample for the diabetic retinopathy analysis consisted of 2,359 subjects.

Table 1 describes the baseline sociodemographic and clinical characteristics for subjects presenting with a baseline PHQ-9 score below 10 and those with a score equal to or greater than 10 (the optimal cut off for major depression). Compared to the group with a total score less than 10, subjects with probable major depression were younger, predominantly female, unmarried, smokers, less active physically, and more obese. Depressed patients also had higher HbA_{1c} levels, were more often on insulin therapy, and had a higher number of complications from diabetes. During the 5-year follow-up period, 22.9% of subjects (n=117) with a probable major depression developed diabetic retinopathy compared to 19.7% (n=363) in the group without depression.

Table 2 presents the estimated odds ratios and hazard ratios for the association between baseline depression severity score and incident diabetic retinopathy. We observed significantly higher odds of diabetic retinopathy in the unadjusted model (OR=1.024), as well as when controlling for the duration of follow-up and sociodemographic baseline characteristics. The magnitude of the association per one point increase in depressive symptoms was small and was slightly decreased when clinical variables were introduced in the model, but strengthened by controlling for health behavior information (OR=1.026, 95% CI (1.002 - 1.051), p=0.033). However, these results suggest that a clinically significant increase of 5 points on the PHQ-9 would be associated with an approximately 15% increase risk of developing diabetic retinopathy. The hazard ratios obtained from the survival analysis indicated a significant association similar to the results observed in the logistic regression analysis. More severe depressive symptoms at baseline were associated with an increased risk of incident diabetic retinopathy (hazard ratios from 1.020 to 1.029) across the four models tested. The magnitude of the association per one point increase in depressive symptoms was small with a fully adjusted hazard ratio of 1.025 but was statistically significant (95% CI (1.009 - 1.041), p = 0.002). Over the 5-year follow-up period, the risk of incident diabetic retinopathy was estimated to be up to 3% higher for each one point increase in depression severity based on the PHQ-9 score.

Discussion

In this prospective population-based cohort study of adults with type 2 diabetes, we found that baseline depressive symptom severity score is associated with a greater risk of diabetic retinopathy. Over a 5-year follow-up period, the risk of incident diabetic retinopathy was estimated to be up to 3% higher for each one point increase in depression severity based on the PHQ-9 score. The results based on survival analysis were also consistent with an approximately 3% increase in risk of retinopathy for every one point increase in depression severity. A clinically significant change in depression has been defined as a change of at least 5 points on the PHQ-9 total score[35]. Thus, for every significant 5-point increase in the severity level of depressive symptoms, the risk of incident diabetic retinopathy would increase by approximately 15%.

The results found in this study are consistent with previous findings on the association between depression and diabetic retinopathy. Several studies have also shown an association between depression and macrovascular and microvascular complications of diabetes [20, 22]. In a prospective study on African Americans with type 1 diabetes, Roy et al. found that depression was associated with a 2.5 increased risk of progression of diabetic retinopathy[31]. Kovacs et al. found that depression was a risk factor for retinopathy in

children with type 1 diabetes[30]. The consistency between the results from these studies and those from the current study reinforces the probability of a significant relationship between depression and incident diabetic retinopathy.

Given that controlling for health risk behaviors did not attenuate the association of depression with incident retinopathy, the correlation observed in this relationship may be potentially explained by physiological changes associated with depression. Depression has been linked to a dysregulation of the hypothalamic-pituitary-adrenal axis, activation of the sympathetic nervous system and an increase in pro-inflammatory factors[5, 6, 39, 40]. The resulting increase in circulating cortisol, catecholamines, cytokines, and platelet and endothelial cell adhesion factors[5, 41, 42] may create an environment promoting increased insulin resistance and glycemic fluctuation[6]. Retinal vessels have been reported to be particularly sensitive to glycemia variability [43, 44] resulting in the appearance of microvascular lesions and neuroretinal damages leading to diabetic retinopathy[23]. Another theory describes the retinal vessels as a reflection of the cerebral microvasculature [45]. In depressed patients, retinopathy could mirror the cerebral microvascular changes associated with depression [25, 46]. Also, health behaviors that were not measured in the current study could be important mediators. For example, depressed patients with diabetes have been described as being reluctant to start insulin when needed[47]. Delaying proper diabetes treatment can also contribute to a higher risk of complications.

Among the limitations of this study, patient recruitment was from one geographic area in one large health system, limiting the generalizability of the results. The drop-off at different stages of the cohort sampling could have led to potential selection bias. The fact that 231 patients did not have a retinal exam during the 5-year follow-up period could have biased our results; however prior research from Group Health has shown no difference in yearly retinal exams by depression status [12]. Depression severity was measured at baseline only which prevented us from assessing if depression status changed during the follow-up period. However, a study on depression course in the same cohort reported a high rate of chronicity of depression at 5 year follow-up[7]. Also, based on initial interview, 75% of subjects with comorbid depression had a history of chronic depression lasting for more than 2 years[7]. Nevertheless, distinguishing a short term depressive episode from a chronic or recurrent episode may have enhanced understanding of how the trajectory of depression symptoms can impact diabetes complications.

This study is the largest prospective cohort study that has been conducted on the association between depression and diabetic retinopathy in patients with type 2 diabetes. Other strengths include the use of a structured tool for the assessment of depression severity and access to medical records, physician diagnoses, automated laboratory, and pharmacy data ensured appropriate verification of clinical information accuracy. We were also able to control for a large number of potential important clinical confounding variables.

This study demonstrates a significant correlation between depression severity and incident diabetic retinopathy, with a risk estimated to increase by up to 15% for each clinically significant increase in depressive symptom severity. This investigation illustrates the need for further exploration of the association between depression and diabetic retinopathy, in order to better understand the biological processes behind this link and to identify potential interventions to prevent diabetic retinopathy.

Acknowledgments

This work was supported by grants from the National Institute of Mental Health (NRSA-T32/MH20021-12, PI: Katon; K24MH069741-07, PI: Katon; RO1MH073686-04, PI: Von Korff).

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FIGURE 1. Recruitment of Pathways Epidemiologic Follow-Up Study cohort to assess diabetic retinopathy incidence

TABLE 1
Baseline characteristics by PHQ-9 scores level

Characteristics	Total sample (N=2,355)			PHQ-9 score < 10 ^a (n=1,843)			PHQ-9 score ≥ 10 ^a (n=512)			Test Statistics	
	Mean	SD		Mean	SD		Mean	SD		F	p
Age (years)	63.9	12.9		64.8	12.7		60.9	13.0		38.17	<0.001
PHQ-9 score	5.7	5.5		3.4	2.7		14.51	4.0		5302.05	<0.001
DCSI	1.1	1.1		1.0	1.1		1.3	1.2		18.55	<0.001
Duration of diabetes (years)	8.1	8.1		8.0	8.2		8.4	7.6		1.03	0.310
HbA _{1c} (%)	7.6	1.4		7.6	1.4		7.9	1.5		16.00	<0.001
BMI (kg/m ²)	31.6	7.2		31.0	6.7		33.9	8.5		69.73	<0.001
Exercise (days/week)	2.7	2.1		2.9	2.1		2.0	2.0		71.71	<0.001
	N	%		N	%		N	%		χ^2	p
Female	1125	47.8		804	43.6		321	62.7		58.41	<0.001
Married	1,586	67.8		1,283	70.1		303	59.8		19.34	<0.001
Non-white	419	17.9		322	17.6		97	19.0		0.55	0.457
Education beyond high school	1,764	75.7		1,394	76.4		310	73.1		2.29	0.130
Requiring insulin therapy	551	23.4		382	20.7		169	33.0		37.71	<0.001
Hypertension	1,451	61.6		1,128	61.2		323	63.1		0.60	0.439
Current smoking	187	7.9		123	6.7		64	12.5		18.61	<0.001

^aTotal score on the PHQ-9 continuous scale

Abbreviations: BMI = body mass index; DCSI = Diabetes Complications Severity Index; HbA_{1c} = glycosylated haemoglobin

TABLE 2
Estimated odds ratios and hazard ratios for the association of baseline depression severity and incident diabetic retinopathy

Covariate adjustment	Odds Ratio		Hazard Ratio	
	OR (95% CI)	p	HR (95% CI)	p
Unadjusted	1.024 (1.006 - 1.042)	0.008	1.025 (1.009 - 1.041)	0.002
Adjusted for:				
length of follow-up	1.025 (1.008 - 1.044)	0.005	1.029 (1.013 - 1.045)	< 0.001
length of follow-up and sociodemographic characteristics ^a	1.029 (1.010 - 1.048)	0.002	1.020 (1.000 - 1.040)	0.053
length of follow-up, sociodemographic characteristics ^a and baseline clinical characteristics ^b	1.023 (1.000 - 1.046)	0.054	1.023 (1.003 - 1.044)	0.026
length of follow-up, sociodemographic characteristics ^a , baseline clinical characteristics ^b and health behaviors ^c	1.026 (1.002 - 1.051)	0.033	1.025 (1.009 - 1.041)	0.002

^aSociodemographic variables included: age, gender, race, education and marital status

^bClinical characteristics included: duration of diabetes, diabetes treatment, hypertension, diabetes complications and enrollment status in the Pathways randomized-controlled trial

^cHealth behaviors included: exercise, smoking, body mass index and HbA_{1c}