Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: August 31, 2023

Citation: Le PH, Olson D, et al., 2023. Relationship between Diabetic Retinopathy Disease Severity, Anxiety, and Depression Medical Research Archives, [online] 11(8). https://doi.org/10.18103/mra.v11i8.4120

DOI
https://doi.org/10.18103/mra.v11i8.4120

ISSN: 2375-1924

RESEARCH ARTICLE

Relationship between Diabetic Retinopathy Disease Severity, Anxiety, and Depression

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ABSTRACT

Purpose: To determine the relationship between nonproliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR), anxiety, and depression.

Materials and Methods: This retrospective case-control study identified patients 18 years or older seen by the University of North Carolina Ophthalmology department between July 2008-July 2018 diagnosed with anxiety, depression, NPDR, and PDR. Odds ratios (OR) were calculated separately for the severity of diabetic retinopathy (DR) and anxiety or depression.

Results: Among the 47,740 study subjects, 27,893 (58%) were female, 3,239 (6.8%) had NPDR and 1,430 (3.0%) had PDR. The incidence of anxiety after DR was 1.5%, and the incidence of depression after DR was 2.4%. NPDR (0.997; 0.896-1.110; $p<0.001$) conveyed no change in odds, while PDR (0.869; 0.756-0.998; $p<0.001$) demonstrated a reduction in odds for a subsequent diagnosis of anxiety. Compared to other 18-34 year old patients with less severe or no disease, 18-34 year old patients with NPDR (2.801; 1.450-5.408; $p=0.003$) and PDR (2.999; 1.499-6.001; $p=0.004$) exhibited an increased odds for subsequent anxiety. NPDR (1.473; 1.342-1.617; $p<0.001$) and PDR (1.232; 1.092-1.389; $p<0.001$) demonstrated an increased odds for subsequent diagnosis of depression. When stratifying by age, 18-34 year old patients again had the highest increase in odds for subsequent diagnosis of depression (NPDR 3.452; 1.774-6.719; $p<0.001$ and PDR 4.382; 2.232-8.603; $p<0.001$).

Conclusions: Patients with DR have an increased risk for a new diagnosis of depression, and DR severity has a positive linear relationship with the diagnosis of depression. Age likely plays a prominent role in risk stratification for a new diagnosis of anxiety in patients with DR.

Keywords: diabetic retinopathy, diabetic retinopathy disease severity, anti-VEGF, anxiety, depression

Introduction

Diabetes mellitus (DM) is a chronic, progressive disease of endocrine origin that damages small blood vessels throughout the body. An estimated 23.1 million people have been diagnosed with diabetes in the United States, and an estimated 7.2 million people are undiagnosed.[1] The ocular manifestations of DM include the spectrum of diabetic retinopathy (DR), the leading cause of vision loss and blindness in the adult United States population.[2] While anti-vascular endothelial growth factor has become an invaluable adjuvant to laser panretinal photocoagulation in treating the late complications of DR, the most crucial and often most challenging treatment is blood glucose and blood pressure control through the use of medications and lifestyle changes. Patients and physicians alike often find it difficult to alter years of habits and behaviors, leading to frustration and discouragement. Medication adherence and overall lifestyle changes, integral to the management of DR, are influenced by the patient's quality of life.[3] Furthermore, a diagnosis of anxiety or depression has been shown to have negative implications on patient quality of life and medication adherence.[4–13]

It is well documented that chronic, progressive eye diseases, such as age-related macular degeneration, glaucoma, and dry eye disease, are associated with comorbid anxiety and depression.[14–16] Furthermore, various studies have investigated the relationship between diabetes mellitus and these mental disorders.[9,17–33] Miyaoka, et al reported a correlation of a depressive state to diabetic complications, particularly DR, in patients in non-insulin dependent diabetics.[19] Poongothai et al likewise described the relationship between depression and diabetic retinopathy in patients with type II diabetes in South India.[18] Oztürk et al investigated specifically the relationship between DM and depression measured by the Geriatric Depression Score (GDS) in the elderly population (mean age of 68.16 years) and found that subjects with diabetic complications, particularly retinopathy, had significantly higher GDS scores.[20] Gorska-Ciebiada et al found similar results in their study that evaluated elderly subjects' cognitive status and psychological state, reporting subjects with diabetic retinopathy have increased odds of having a comorbid mild cognitive impairment and high GDS scores.[21] Kalantari, et al also identified diabetic retinopathy as a risk factor for depression in their cross-sectional study of type II diabetic patients.[23] Xu et al studied subjects with type II diabetes and found that poor vision in the better-seeing eye and history of laser treatment were significantly associated with depression.[34] Trento et al also found that subjects with decreased vision secondary to diabetic retinopathy had worse scores on the quality of life survey when compared to patients without vision loss.[27]

Not all studies have demonstrated a significant relationship between DR and depression or decreased quality of life. Karlson and Agardh analyzed a young cohort of insulin-dependent diabetic subjects and found no significant correlation between diabetic symptoms and late complications of diabetes, including retinopathy and neuropathy.[31] Hirai et al found that visual acuity and diabetic retinopathy status did not significantly impact the quality of life scores in 520 type I diabetic subjects.[35]

Although limited by study design elements, such as relying on questionnaires and population demographics, two studies have commented on DR severity and quality of life, and depressive symptoms.[25,28,36]

Mazhar et al investigated the relationship between DR severity and subject reported quality of life. Using a severity scale ranging from no diabetic retinopathy (1) to bilateral proliferative diabetic retinopathy (PDR) (15), linear regression models were used to evaluate for relationships between DR severity and subject quality of life measured using the health-related quality of life and National Eye Institute Visual Function Questionnaire surveys.[25] This study group found a gradual decline in HRQOL in the early stages of the disease that became much more drastic as the disease progressed, specifically after the patient had been diagnosed with moderate NPDR in both eyes. While it can be inferred that decreased HRQOL scores may correspond with increased levels of anxiety and depression, this was not explicitly investigated in their study.

Hirai et al investigated the rates of depression in subjects with type I diabetes.[35] This study included 484 subjects from the Wisconsin Epidemiologic Study of Diabetic Retinopathy who provided information on the 25-year follow up questionnaire. Subjects were divided into three groups based on their severity of diabetic eye disease: none-mild non-proliferative diabetic retinopathy (NPDR), moderate-severe NPDR, and PDR. There was no statistically significant relationship between these groups, though clinically, the group with PDR appears to have increased rates of depressive symptoms. Of note, this study found women with type I diabetes to have increased rates of depression or depressive symptoms based on anti-

depressive medications and the results of the Center for Epidemiologic Studies Depression questionnaire.

Few studies have investigated the relationship between DR and anxiety. Rees et al analyzed 519 subjects with diabetes to investigate the relationship between diabetic retinopathy severity and comorbid anxiety and depression.[36] They did not find a significant relationship between DR and anxiety but found anxiety associated with a prior diagnosis of anxiety and younger age. They also found that patients with severe NPDR and PDR, but not mild NPDR or moderate NPDR, were significant risk factors for depressive symptoms. Subjects with diabetic macular edema were not found to be at increased risk of depressive symptoms.

Given that DR has a broad spectrum of disease presentation, further elucidating the relationship between DR severity and mental illness is necessary. Therefore, our study aims to investigate associations between DR severity, anxiety, and depression in a large population.

Materials and Methods

In our retrospective chart review, we utilized the Carolina Data Warehouse for Health (CDWH), a de-identified repository of medical records of patients seen at a University of North Carolina hospital or outpatient clinics, to identify subjects 18 years and older evaluated by the Ophthalmology department. This study was deemed exempt from obtaining consent during its approval from the University of North Carolina Institutional Review Board and adhered to the tenets of the Declaration of Helsinki. Subjects were identified with diagnoses of DR, anxiety, depression, and any combination of these diseases between July 2008-July 2018 using the International Classification of Disease (ICD-9 and ICD-10) diagnostic codes. The specific codes used can be found in Table 1. Subjects were stratified by disease severity, including no DR, nonproliferative diabetic retinopathy (NPDR), and proliferative diabetic retinopathy (PDR). Subjects were also stratified by sex and age (18-34 years old, 35-54 years old, 55-64 years old, and ≥65 years old). Patients with other severe ophthalmic disease were not excluded to maximize the pragmatic nature of our results and provide effect size calculations in the context of ophthalmic patients seen at a tertiary educational hospital system.

STATISTICAL ANALYSIS

Comparisons of categorical variables were made using the Fisher-exact test and chi-square test. Multiple logistic regression was used to calculate odds ratios (OR) adjusted for age and sex. All patients with pre-existing diagnoses of anxiety or depression before being diagnosed with DR were excluded from multiple logistic regression analysis. Patients with a diagnosis of anxiety or depression after diagnosis of DR were allocated according to the level of DR severity at the time of the mental health diagnosis. Further stratifications of age and sex were compared between patients of similar age or sex characteristics. Age group stratification was categorical due to restraints of the de-identified data within the CDWH. All data were analyzed using Statistical Analysis Software (SAS) (Cary, NC).

Results

Table 1 includes the study population demographics and descriptive statistics. Among the 47,740 study subjects, 27,863 (58%) were female, 3,239 (6.8%) had NPDR and 1,430 (3.0%) had PDR. The prevalence of anxiety in the study population was 21.7%, and the prevalence of depression was 22.5%. The incidence of anxiety after DR was 1.5%, and the incidence of depression after DR was 2.4%. Table 2 shows the calculated ORs between levels of severity of DR and anxiety, and by age group and sex.

ANXIETY AND DIABETIC RETINOPATHY

There was no statistically significant difference in the odds of a subsequent diagnosis of anxiety in patients with NPDR than in patients with no DR (0.997; 0.896, 1.110; p<0.001). However, there was a statistically significant lower odds of being diagnosed with anxiety in patients with PDR than in patients with NPDR and no DR (0.869; 0.756, 0.998; p<0.001). (Table 2)

In 18-34 year olds, the odds of anxiety increased with increasing severity level of DR; NPDR (2.801; 1.450, 5.408; p<0.003) and PDR (2.99; 1.499, 6.001; p< 0.004). In 35-54 year olds, there was no difference in the odds of anxiety among the severity comparisons of DR; NPDR (1.256; 0.986, 1.601; p<0.001) and PDR (0.918; 0.703, 1.200; p<0.001). In 55-64 year olds, the odds of being diagnosed with anxiety were lower in PDR than in patients with NPDR and no DR (0.660; 0.498, 0.875; p=0.001). There was no difference in the odds of being diagnosed with anxiety in 55-64 year olds with NPDR (0.993; 0.807, 1.224; p<0.001) compared to those without NPDR. In patients 65 years old and older, there was no difference in the odds of anxiety among the severity comparisons of DR; NPDR (0.884; 0.761, 1.027; p=0.024) and PDR (0.909; 0.738, 1.121; p< 0.012). (Table 2)

Table 1: Study Population Demographics and Descriptive Statistics (N = 47,740)

	N (%)
Sex	
Female	27,863 (58)
Male	19,877 (42)
Age	
18-34	6588
35-54	11491
55-64	8749
65+	20912
Clinical Diagnoses	
Anxiety [a]	10,372 (21.7)
Depression [b]	10,760 (22.5)
Diabetic Retinopathy [d]	
NPDR	3,239 (6.8)
PDR	1,430 (3.0)
Anxiety after DR	832 (1.5)
Depression after DR	1,331 (2.4)

International Classification of Disease (ICD) Codes: a - ICD9: 300.0; ICD10:F41.X; b - ICD9:311, 296.2X, 296.3X; ICD10:F32.X, F33.X; c - ICD-9: 250.X, ICD-10: E10, E11; d - ICD-9: 362.01, 362.01, 362.03, 362.04, 362.05, 362.06, 362.02; ICD-10: E10.311, E10.319, E11.311, E11.319, E13.311, E13.319, E10.311, E10.319, E11.311, E11.319, E13.311, E13.319, E10.321, E10.329, E11.321, E11.329, E13.321, E13.329, E10.331, E10.339, E11.331; e – ICD9 362.07; ICD-10 E11.311.

Table 1: Estimated Odds Ratio between Levels of Severity of Diabetic Retinopathy and Anxiety and Depression, by Age Group and Sex

	Anxiety			Depression		
	Adjusted OR	*95% CI*	*p-value*	*Adjusted OR*	*95% CI*	*p-value*
Disease						
NPDR	0.997	0.896, 1.110	<0.001	1.473	1.342, 1.617	<0.001
PDR	0.869	0.756, 0.998	<0.001	1.232	1.092, 1.389	<0.001
Age						
18-34						
NPDR	2.801	1.450, 5.408	0.003	3.452	1.774, 6.719	<0.001
PDR	2.999	1.499, 6.001	0.004	4.382	2.232, 8.603	<0.001
35-54						
NPDR	1.256	0.986, 1.601	<0.001	1.468	1.164, 1.852	<0.001
PDR	0.918	0.703, 1.200	<0.001	1.277	1.001, 1.630	<0.001
55-64						
NPDR	0.993	0.807, 1.224	<0.001	1.572	1.315, 1.879	<0.001
PDR	0.660	0.498, 0.875	0.001	1.054	0.839, 1.324	0.067
65+						
NPDR	0.884	0.761, 1.027	0.024	1.394	1.229, 1.580	<0.001
PDR	0.909	0.738, 1.121	0.012	1.244	1.040, 1.488	0.001
Sex						
Female						
NPDR	0.990	0.864, 1.135	<0.001	1.471	1.302, 1.662	<0.001
PDR	0.922	0.774, 1.099	<0.001	1.163	0.909, 1.365	<0.001
Male						
NPDR	1.01	0.850, 1.201	<0.001	1.478	1.279, 1.707	<0.001
PDR	0.79	0.628, 0.994	<0.001	1.334	1.113, 1.600	<0.001

In females, there was no difference in the odds of anxiety among the severity comparisons of DR; NPDR (0.990; 0.864, 1.135; p<0.001) and PDR (0.922; 0.774, 1.099; p<0.001). In males, the odds of anxiety were lower in PDR (0.79; 0.628, 0.994; p<0.001) than in those with less severe or no DR. Furthermore, there was no difference in the odds of anxiety when comparing NPDR (1.01; 0.850, 1.201; p<0.001) to those without DR. (Table 2)

DEPRESSION AND DIABETIC RETINOPATHY

The odds of being diagnosed with depression increased with increasing levels of DR severity; NPDR (1.473; 1.342, 1.617; p<0.001) and PDR (1.232; 1.092, 1.389; p<0.001). Table 2 shows the estimated ORs between levels of severity of DR and depression by age group. (Table 2)

Age groups of 18-34 year olds (NPDR: 3.452; 1.774, 6.719; p<0.001 and PDR: 4.382; 2.232, 8.603; p< 0.001), 35-54 year olds (NPDR: 1.468; 1.164, 1.852; p<0.001 and PDR: 1.277; 1.001, 1.630; p< 0.001), and ≥65 year olds (NPDR: 1.394; 1.229, 1.580; p<0.001 and PDR: 1.244; 1.040, 1.488; p=0.001) reveal the odds of depression increased with increasing severity level of DR. However, within 55-64 year olds, there was an increased odds of depression in NPDR (1.572; 1.315, 1.879; p<0.001) compared to those without DR, but there was no difference in the odds of being diagnosed with depression in PDR (1.054; 0.839, 1.324; p=0.067) compared to less severe or no DR. (Table 2)

In females, there was only an increase in the odds of depression when investigating NPDR (1.471; 1.302, 1.662; p<0.001) as the calculated OR for PDR was 1.163 (0.9092, 1.365; p<0.001). In males, the odds of depression increased with increasing severity level of DR; NPDR (1.478; 1.279, 1.707; p<0.001) and PDR (1.334; 1.113, 1.600; p<0.001). (Table 2)

Discussion

Evaluation of anxiety and DR severity in this study suggests that patients 18-34 years old have an increased risk for a subsequent diagnosis of anxiety when exposed to NPDR. Furthermore, such risk is intensified with progression to PDR. The heightened risk among 18-34 year old patients is in the setting of an elevated anxiety prevalence within the age group and is a relationship supported by other studies that also investigated the association between anxiety and diabetes or DR.[37–40] This association encourages increased awareness of patients within this age range and exemplifies the importance of multidisciplinary care to avoid negative implications of anxiety on patient care and overall quality of life.

When accounting for age and sex during regression analysis, exposure to NPDR does not influence the risk of subsequent anxiety diagnosis. In contrast, exposure to PDR reduces the risk of subsequent anxiety diagnosis. Although sex does not appear to play a role in this outcome, a component of these findings can be attributed to the protective effect seen from older age as exposure to NPDR or PDR confers either no change or reduction in risk for subsequent diagnosis of anxiety in all older age groups. Rees et al. also observed a similar effect in older patients with DR, and geriatric literature would suggest it stems from improved coping abilities.[37,40–42] Furthermore, it is necessary to note that the decreased risk of subsequent anxiety is within the context of being compared to patients of less severe disease and patients with other ophthalmic conditions aside from DR. Thus, the association between PDR and anxiety can be interpreted as support for allocation of more anxiety-related resources towards patients with other ocular diseases associated with anxiety, such as glaucoma or age-related macular degeneration, compared to patients with DR.[14,15]

Consistent with other investigations of DR and depression, our study also shows an association between DR and depression.[17–23,36,43] However, our study further expands upon the relationship by demonstrating further compounding of risk for subsequent depression following progression to PDR. Our findings are supported by those reported by Rees et al., but contradict the conclusions drawn by Hirai et al.[37,44] Hirai et al. reported no significant relationship when investigating the rates of depression using the Center for Epidemiologic Studies Depression questionnaire in patients with a 25-year history of type I diabetes with various severities of DR.[28] Interestingly, Rees et al. evaluated patients with both type 1 and type 2 patients, similar to our study, while Hirai et al. only studied patients with type 1 diabetes mellitus. This suggests the diagnosis of diabetes mellitus may influence the association between DR severity and depression. Nevertheless, other distinct differences in study design, such as categorization by depressive symptoms with a questionnaire known not to be used alone as a diagnostic tool, not accounting for pre-DR depression, and no assessment of temporality between DR and depression, may also explain the differences between study results.[45]

Similar to findings in anxiety, the risk for depression due to exposure to NPDR or PDR is highest in the age group of 18-34. However, unlike anxiety, increased risk of depression persists across all age groups and regardless of DR severity (except 55-64 year olds with PDR due to insufficient sample size). The persistence of increased risk for subsequent depression diagnosis in older age groups is consistent with studies by Oztürk et al. and Gorska-Ciebiada and associates, who found that subjects with DR had worse results Geriatric Depression Scores (GDS) in their geriatric study populations [20,21]. Furthermore, it aligns with

generalized research on depression that found depression is not known to be influenced by age but rather the health disparities commonly linked to age.[46]

Concerning the influence of sex, our study revealed that men had an increased risk of depression that increased with DR severity when compared to their age-matched controls with less severe or no DR. This aligns with the findings that men are more likely to have depressive symptoms secondary to a separate comorbid disease [47]. However, the female group only exhibited an increased risk of depression compared to females without DR. Although exposure to PDR does not change the risk compared to those with less severe or no DR, these findings emphasize the inclusiveness of the increased risk across both sexes.

Our study's findings on the relationship between DR severity and depression carry potential implications in managing patients with DR and prompt consideration of the bi-directional relationship between diabetes and depression. Both Ishizawa and colleagues and Black et al. found that worsening depression scores increased the odds of having diabetic complications, including retinopathy. In addition, Roy et al. found that worse scores in the Beck Depression Inventory (BDI), which translates to more severe depressive symptoms, were associated with worse glycemic control and a higher risk of retinopathy progression in African Americans with Type I diabetes [48]. Further, Yekta and coworkers found that in patients with a known diagnosis of diabetes, those taking an antidepressant medication were at decreased odds of having DR compared to those who were not.[49] In addition to blood glucose and blood pressure control, recognizing that underlying depression may be a major contributing factor to the progression of diabetic eye disease further illuminates the importance of a multidisciplinary approach to managing diabetes and its complications.

Due to the nature of our retrospective case-control design, we are limited in our ability to determine causality within the relationship between DR severity, anxiety, and depression. However, our selection of positive outcomes requiring anxiety/depression diagnosis to follow the diagnosis of DR bolsters the validity of our findings. Furthermore, our ample sample size yielded results previously not described with excellent statistical power. Additionally, although the CDWH reports on a single hospital system and limits our subject population to a single geographical area, the University of North Carolina has hospitals throughout North Carolina, draws from diverse ethnic and socioeconomic backgrounds, and allows our results to be generalizable to larger populations.

Conclusion

Our large population study suggests an increased risk in the subsequent diagnosis of depression in patients with NPDR, and patients with PDR are at an even increased risk. These associations should be considered as we diagnose and care for individuals with diabetic eye disease. While our study revealed many interesting relationships regarding age and sex, these were not the primary aim of our study, and additional investigation is merited to understand these associations further. Future prospective investigations are needed to provide more insight into the causal relationship between DR and mental health illness.

Acknowledgments

a. Funding/Support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

- The statistical support for this research was provided by the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH), through Grant Award Number UL1TR002489. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

b. Financial Disclosures: The authors have no financial disclosures.

c. Other Acknowledgements: none.

Declaration of Interest Statement

The authors report no conflicts of interest. This work has not been published elsewhere and has not been submitted simultaneously for publication elsewhere.

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