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Risk Factors for Proliferative Diabetic Retinopathy in a Latino American Population

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Abstract

Objective—To assess the personal and demographic risk factors for proliferative diabetic retinopathy (PDR) in Latino Americans in Los Angeles County.

Design—A prospective, non-interventional, cross-sectional case control study.

Participants—Seven hundred and twenty nine subjects from Los Angeles County University of Southern California Medical Center (LAC+USC), Los Angeles, CA, were enrolled.

Methods—All patients were recruited prospectively from the LAC+USC Medical Center and affiliated clinics between June 2008 and June 2011. Complete personal data and results from systemic and ophthalmic examinations were collected for all enrolled subjects. Laboratory tests such as glycosylated hemoglobin, creatinine levels, and cholesterol levels were collected prospectively by drawing blood at the time of each patient's clinic visit.

Main Outcome Measures—Age, gender, type of diabetes mellitus (DM I or II) duration of DM, history of hypertension, history of insulin use, height, weight, and body mass index, smoking history, glycosylated hemoglobin, creatinine levels, and cholesterol levels.

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Results—The mean age of subjects with no diabetic retinopathy was 56.38 years (standard deviation [SD], 10.16), while that of patients with PDR was 57.43 years (SD, 9.63). Parameters that conferred a statistically significant increased risk for PDR in the multivariate model included gender (men were at higher risk: odds ratio (OR), 4.11; 95% confidence interval (CI), 2.56–6.58), insulin use (OR, 1.85; 95% CI, 1.13 – 3.03), history of hypertension (OR, 1.64; 95% CI, 1.02 – 2.63), and duration (>25 years versus 10 to 15 years) of diabetes (OR, 22.00; 95%CI, 9.76 – 49.60).

Conclusions—In this case-control study in a Latino population, duration of diabetes and male gender were the strongest risk factor for the development of PDR followed by insulin use, and hypertension. Interestingly, smoking and glycosylated hemoglobin levels did not confer additional significant risk in this cohort.

Keywords

Diabetes mellitus; Proliferative diabetic retinopathy; Diabetic retinopathy; Risk factors; Latinos; Hispanic Americans

Proliferative diabetic retinopathy (PDR) is a serious complication of diabetes and is a leading cause of legal blindness and visual impairment in the working age population of western countries.[1–3] In the United States (US), Latinos have a high prevalence of diabetes mellitus (DM) and appear to be at high risk for microvascular complications, including DR.[2,4–6] In addition, the Latino population is the largest and fastest growing minority group in the US (with 50.5 million people, accounting for 16.3% of population).[2] The prevalence of DR is 2 to 2.5 times greater in this population group than in other US population groups.[5] The rate of complications from diabetes in the Latino community is also high, although the reported prevalence of retinopathy has varied among previous studies.[2,5,–7]

The risk factors for developing any DR have been well described in previous studies.[8–12] A longer duration of diabetes, hypertension, and elevated glycosylated hemoglobin, have been identified as consistent risk factors.[10–13] The Early Treatment Diabetic Retinopathy Study group has reported that the type of diabetes, body weight, and the age of the patient are also important risk factors for developing PDR in particular.[8] Risk factors for progression to PDR in particular are of importance, given the risk for severe vision loss in patients with advanced disease. Several previous studies have reported risk factors for DR in a general population, including a number of different ethnicities; and a few studies have reported the risk factors for PDR in selected subsets of these large cohorts.[7, 8, 12] To our knowledge, the risk factors for developing PDR specifically (as opposed to any retinopathy) in an exclusively Latino population have not been described. In this report, we explore this issue in a case-control study (subjects with PDR defined as cases and subjects with diabetes for at least 10 years but no or minimal DR defined as controls) to determine the personal and demographic risk factors for PDR in Latino Americans in Los Angeles County.

Research Design and Methods

A total of 1115 Latino patients with DM participated in this prospective case control study. The primary objective of the study was to determine the genetic susceptibility for

development of PDR, with the secondary goal of identifying other risk factors in this population. Patients were recruited prospectively from the Los Angeles County University of Southern California (LAC+USC) Medical Center ophthalmology clinics between June 2008 and June 2011. There was no age criterion for enrollment in the study; but all subjects self-identified as Latinos and had a known diagnosis of DM, previously confirmed by laboratory testing by their primary care physician. All patients gave written informed consent and agreed to have their blood drawn for genetic analysis. Seven-field color fundus photographs and spectral domain optical coherence tomography were also obtained. The study protocol was approved by the Institutional Review Board of the University of Southern California, and the study adhered to the recommendations of the Declaration of Helsinki.

Since a case-control design was planned, two sub-cohorts of Latino patients with DM were recruited. One cohort (the cases) consisted of individuals with a confirmed diagnosis of PDR and a known diagnosis of DM for at least 10 years. The control cohort consisted of individuals with a known diagnosis of DM for at least 10 years and no evidence of DR or only minimal nonproliferative DR (per modified Airlie House classification). The diagnosis of PDR or absence of DR was made by biomicroscopic examination by an ophthalmologist and subsequently confirmed by review of 7-field color photographs at the Doheny Image Reading Center.

Data Collection

A number of prespecified personal, demographic, ophthalmic, and laboratory variables were collected for each subject. Data was collected from the LAC+USC medical and laboratory records, as well as by subject interviews. Collected variables included age, gender, type of DM (I or II) duration of DM, history of hypertension (as determined by the patient's internist), history of insulin use (based on history of using), height, weight, and body mass index (BMI). Smoking history (including duration and amount) was collected, and both current and former smokers were considered to be smokers for subsequent statistical analysis. Laboratory variables ascertained included the patient's most recent (within 30 days of enrollment) glycosylated hemoglobin, serum creatinine, and serum cholesterol. Ophthalmic data collected included prior ocular history (including history of surgery before onset of PDR) and associated comorbid ocular diseases, best-corrected visual acuity, slit-lamp biomicroscopic findings (including cataract), and dilated indirect ophthalmoscopic findings. Seven-field color fundus photographs and macular spectral domain optical coherence tomography data from both eyes were exported for masked grading at the Doheny Image Reading Center. Blood was also collected for genetic analyses to be completed at a later date. With BMI calculated as weight (kg)/height (m) squared, obesity was defined as BMI ≥ 30 in accordance with previous studies.[14] Using LAC+USC Medical Center guidelines, we considered an A HbA1c value of greater than 7.0% was deemed to signify inadequately controlled diabetes (similar to the Diabetes Control and Complications Trial criteria).[15] Based on laboratory guidelines, we considered a creatinine value of >1.2 mg/dL as abnormal; and a serum cholesterol value of >200 mg/dL was considered evidence of hypercholesterolemia (Table 1).

Cohort for Analysis

Among the total cohort of 1115 subjects, complete data were available for all prespecified variables described above in only 729 persons (65.38%). In the remaining 386 persons, one or more outcome measures (such as cholesterol within 30 days of enrollment, etc) were missing, and these individuals were not included in the subsequent analyses described in this report. Among the 729 subjects constituting the analysis cohort, 419 (57%) were cases (PDR in at least one eye) and 310 (43%) were controls (no or minimal retinopathy, duration of DM > 10 years). Among the PDR cases, 398 (95%) had PDR in both eyes.

Statistical Analysis Methods

Statistical analyses were performed using SPSS for Windows version 18.0 (SPSS Science, Chicago, IL). For continuous variables, the results were expressed as mean ± standard deviation (SD). Student's *t*-test was used for comparisons between cases and controls. For categorical variables, results were expressed as a percentage of the total. The chi-square test was used to compare proportions among groups. For ocular parameters, generalized estimating equations were used to account for interactions between the two eyes of a patient. Univariate and multivariate logistic regression analysis was performed to study the effect of various risk factors, using the presence of PDR as a dependent variable. From the univariate analysis, variables with *P* values of ≤ 0.05 and those that were already established as risk factors in prior large studies (discussed in Introduction) were included in the multivariate logistic regression analysis to derive the final model. A *P* value ≤ 0.05 was considered significant.

Results

A total of 729 patients (287 males, 40%) between the ages of 14 and 92 years (median = 58) were included in the final analysis. There was no age difference between the case and control cohorts: the mean age of subjects with no DR was 56.38 years (SD, 10.16), while that of patients with PDR was 57.43 years (SD, 9.63). We compared the characteristics of those with PDR to those with no DR (Table 1). There was a significant proportional gender difference between the study cohorts, with a higher percentage of males in the PDR cohort. Most of the subjects with PDR in this cohort were on insulin treatment. Persons with PDR were also more likely to have hypertension. There were significantly more type 1 diabetics in the PDR case cohort than in the no DR control cohort. Descriptive and comparative results of quantitative parameters of the study cohorts are summarized in Table 2. Of note, BMI was statistically significantly lower in the PDR cohort than in the no DR controls although the actual difference was small. Levels of glycosylated hemoglobin, serum creatinine, and total cholesterol were significantly higher in subjects with PDR than in those without PDR. Not surprisingly, individuals with PDR had significantly lower visual acuity.

The results of the univariate and multivariate models are shown in Table 3. In the univariate analysis, PDR was associated with male gender (*P* <0.001), insulin treatment (*P* <0.001), smoking (*P* 0.054), hypertension (*P* <0.001), a > 10 year duration of DM (*P* <0.001), and obesity (*P* <0.001). Significant factors with a *P* value ≤ 0.05 were included in the multivariate analysis. Again, male patients appeared to have a significantly increased risk of

PDR (odds ratio [OR] = 4.11; 95% confidence interval (CI): 2.56 – 6.58, P <0.001), as did patients who used insulin (OR=1.85; 95% CI: 1.13 – 3.03, P = 0.02) or patients who had hypertension (OR = 1.64; 95% CI: 1.02 – 2.63, P = 0.04). Subjects with a > 25-year duration of DM were at higher risk of PDR (OR = 22.00, 95% CI: 9.67 – 49.60, P <0.001) when compared to subjects with a 10- to 15-year duration of DM. Interestingly, individuals who were obese (OR = 0.49, 95% CI: 0.25 – 0.96, P = 0.04) were less likely to have PDR. High creatinine levels were also associated with PDR (OR 6.43, 95% CI: 1.12 – 34.12, P = 0.03). Factors such as glycosylated hemoglobin did not remain as independent risk factors for PDR in the multivariable models. Total cholesterol was not a risk factor in either of univariate and multivariate analysis.

Discussion

In this study of Latino diabetics, male gender, insulin treatment, hypertension, and longer duration of diabetes were found to be associated with the development of PDR. Latino males were at four times greater risk of developing PDR when compared to females, which may be similar to studies in other populations.[16,17] In the current study, individuals on insulin treatment were at high risk of progression to PDR, might be because their diabetes was more severe and their glycemic control was poorer.[7] Smoking has historically not been shown to be a strong risk factor for developing PDR.[8,16] Similarly, in our study, patients with a history of smoking showed less risk of developing PDR, although the risk of developing PDR was higher in those individuals who smoked a larger number of cigarettes per day (OR 1.58)[8,16]; but this did not remain as an independent risk factor in the multivariate analysis.

Our findings in this Latino cohort appear consistent with previous studies which observed that hypertension and duration of diabetes were related to PDR.[7–9,12,16] Latinos with hypertension in our cohort are at 1.64 times the risk of developing PDR compared to Latinos with no hypertension. Patients with a longer duration of diabetes have a more than twentyfold greater risk of developing PDR compared to those with a 10- to 15-year duration.

A negative association between BMI and PDR was observed in this study cohort. Many epidemiologic studies have shown an inconsistent relationship between BMI and DR.[18] Some of these studies have reported positive associations between high BMI and DR.[19–21] However, in our study, individuals with a higher BMI seemingly had a lower risk of developing PDR. Obesity (BMI ≥ 30) also remained significant in the final model as an independent protective factor, but the odds ratio (OR = 0.49) was lower when compared to overweight but not obese persons (BMI 25–29.9; OR = 0.62). A similar negative association between BMI and DR has been reported in other population-based studies.[8, 14, 22, 23]

Factors such as glycosylated hemoglobin levels, creatinine levels, and cataract surgery were also observed to be significant risk factors in the univariate model. While a history of cataract surgery and higher creatinine levels remained independent risk factors in the multivariable model, glycosylated hemoglobin was no longer significant. It is worth noting, however, that glycosylated hemoglobin was based on the most recent (within 30 days of enrollment) level available in each patient's laboratory record. Average levels over an extended period of time or over the entire duration of the patients' diabetes were not

available. Patients with PDR may have had much higher levels in the past. It is interesting that cholesterol levels were not a significant predictor of PDR in our study.

Our study is not without limitations. Although the subjects were recruited prospectively, some of the laboratory data was collected retrospectively; long-term averages for these laboratory values (such as glycosylated hemoglobin) were not available. In addition, the complete data was not available for a significant proportion of the subjects (almost 35%) who were thus not included in these analyses. This creates a potential selection bias, although comparison between this excluded cohort and the included cohort on available variables did not demonstrate any significant differences. Furthermore, although smoking status was available for the included cohort, detailed quantitative pack-year information was only available on a subset. Despite these limitations, our study has many strengths, including the large sample size of individuals with PDR, standardized laboratory assessment of serum samples and imaging data, and reading center confirmation of cases and controls.

In summary, our data show a number of strong risk factors for developing PDR in Latinos, including age, male gender, insulin treatment, history of hypertension, and duration of diabetes. To our knowledge, this is the first study reporting the risk factors specifically for the development of PDR in a Latino population. These observations may be of value in future investigations, particularly as the Latino population in the US is expected to double by the year 2025.

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Summary statement

In a Latino population, duration of diabetes was the strongest risk factor for the development of PDR. Interestingly, smoking and glycosylated hemoglobin levels did not confer additional significant risk in this cohort.

Table 1

Sample Distribution of Study Parameters among Study Groups

Variable	Sample with no DR (N = 310), n (%)	Sample with PDR (N = 419), n (%)	*P* value
Age (Years)			
< 40	24 (7.7)	19 (4.5)	
40–49	52 (16.8)	66 (15.8)	
50–59	97 (31.3)	145 (34.6)	
60–69	117 (37.7)	156 (37.2)	
>69	20 (6.5)	33 (7.9)	0.32
Gender			
Male	91 (29.4)	196 (46.1)	
Female	219 (70.6)	226 (53.9)	<0.001
Insulin treatment			
No	242 (78.1)	180 (43)	
Yes	68 (21.9)	239 (57)	<0.001
Smoking status			
No	245 (79)	305 (72.8)	
Yes	65 (21)	114 (27.2)	0.054
Number of cigarette packs (n = 63 for with no DR group; n = 109 for PDR group)			
<0.5 pack/day	24 (7.7)	29 (6.9)	
≥0.5 – ≤1 pack/day	17 (5.5)	36 (8.6)	
>1 pack/day	22 (7.1)	44 (10.5)	0.21
History of hypertension			
No	149 (48.1)	102 (24.3)	
Yes	161 (51.9)	317 (75.7)	<0.001
Type of DM			
Type 1	10 (3.2)	75 (17.9)	
Type 2	300 (96.8)	344 (82.1)	<0.001
Duration of DM			
10–15 yrs	227 (73.2)	93 (22.2)	
16–20 yrs	53 (17.1)	131 (31.3)	
21–25 yrs	18 (5.8)	98 (23.4	
>25 yrs	12 (3.9)	97 (23.2)	<0.001

DM-diabetes mellitus; DR-diabetic retinopathy; PDR-proliferative diabetic retinopathy;

Table 2

Comparison of Quantitative Parameters Between Study Groups

	No DR (mean ± SD)	With PDR (mean ± SD)	*P* value
Age (Years)	56.38 ± 10.16	57.43 ± 9.63	0.22
BMI	30.77 ± 6.33	29.14 ± 5.72	0.05
HbA1c (%)	7.87 ± 1.64	8.69 ± 2.07	0.02
Creatinine (mg/dL)	0.73 ± 0.36	1.56 ± 1.93	<0.001
Total cholesterol (mg/dL)	179.12 ± 48.69	183.43 ± 57.81	0.29
Visual acuity (Log MAR)			
Right Eye	0.27 ± 0.46	0.86 ± 0.82	<0.001
Left Eye	0.25 ± 0.32	0.79 ± 0.75	<0.001
Duration of DM (years)	13.72 ± 4.42	20.88 ± 7.51	<0.001

DR-diabetic retinopathy; PDR-proliferative diabetic retinopathy; BMI-body mass index; MAR-minimum angle of resolution; DM-diabetes mellitus;

Table 3

Regression Analysis to Study the Effect of Various Risk Factors on Proliferative Diabetic Retinopathy

	Univariate Analysis			Multivariate Analysis		
Risk Factor	***Odds Ratio***	**95% CI**	***P* Value**	***Odds Ratio***	**95% CI**	***P* Value**
Age (Years)						
< 40	1			1		
40–49	1.6	0.79 – 3.24	0.19	1.16	0.35 – 3.84	0.81
50–59	1.89	0.98 – 3.63	0.06	1.52	0.50 – 4.67	0.47
60–69	1.68	0.88 – 3.22	0.12	1.05	0.34 – 3.25	0.93
>69	2.08	0.92 – 4.73	0.08	1.31	0.35 – 4.99	0.69
Gender						
Female	1			1		
Male	2.1	1.51 – 2.81	< 0.001	4.11	2.56 – 6.58	< 0.001
Insulin Treatment						
No	1			1		
Yes	4.73	3.39 – 2.81	< 0.001	1.85	1.13 – 3.03	0.02
Smoking status						
No	1			1		
Yes	1.14	0.99–1.99	0.054	0.90	0.57–1.40	0.63
History of Hypertension						
No	1			1		
Yes	2.88	2.10 – 3.94	< 0.001	1.64	1.02 – 2.63	0.04
Duration of DM						
10 – 15 yrs	1			1		
16–20 yrs	6.03	4.04 – 9.00	< 0.001	8.41	4.79 – 14.77	< 0.001
21–25 yrs	13.29	7.61 – 23.21	< 0.001	20.34	9.70 – 42.66	< 0.001
>25 yrs	19.73	10.34 – 37.66	< 0.001	22	9.76 – 49.60	< 0.001
BMI						
Normal (18.5 – 24.9)	1			1		
Over weight (25 – 29.9)	0.59	0.38 – 0.92	0.02	0.62	0.32 – 1.18	0.15
Obese ≥30	0.45	0.29 – 0.70	< 0.001	0.49	0.25 – 0.96	0.04

	Univariate Analysis			Multivariate Analysis		
Risk Factor	***Odds Ratio***	**95% CI**	***P* Value**	***Odds Ratio***	**95% CI**	***P* Value**
DM type						
Type I	1			1		
Type II	0.15	0.08 – 0.30	< 0.001	0.27	0.10 – 0.70	0.007
Cataract Surgery						
No	1			1		
Yes	2.36	1.37 – 4.06	0.02	4.69	1.13 – 19.45	0.03
HbA1C						
≤7.0 (normal)	1			1		
>7.0 (abnormal)	2.18	1.38 – 3.45	0.001	2.5	0.79 – 7.91	0.12
Creatinine						
≤ 1.2 (normal)	1			1		
> 1.2 – ≤2.4	14.53	6.22 – 33.91	< 0.001	6.43	1.12 – 34.12	0.03
Total Cholesterol						
≤ 200 (normal)	1			1		
> 200 – ≤300	1.17	0.73 – 1.88	0.52	0.46	0.13 – 1.60	0.22

Factors with significant levels ≤ 0.05 in univariate model were adjusted for multivariate model; CI: confidence interval; DM: diabetes mellitus; BMI: body mass index; HbA1C: glycosylated hemoglobin

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