

Biologic Risk Factors Associated with Diabetic Retinopathy

The Los Angeles Latino Eye Study

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Objective: To identify biologic risk factors associated with having diabetic retinopathy (DR) in Latinos with type 2 diabetes mellitus (T2DM).

Design: Population-based cross-sectional study.

Participants: Six thousand three hundred fifty-seven Latinos ages ≥ 40 years from 6 census tracts in Los Angeles, California.

Methods: An in-home interview was administered to all participants in the Los Angeles Latino Eye Study (LALES). All participants diagnosed with T2DM underwent a complete ophthalmologic examination including stereoscopic fundus photography (7 standard Early Treatment Diabetic Retinopathy Study fields). Photographs were graded in a masked manner using a modified Airlie House grading system to assess presence and severity of DR. Univariate and stepwise logistic regression analyses were used to identify independent risk factors.

Main Outcome Measures: Biologic risk factors associated with any DR and proliferative DR (PDR).

Results: Of the 7789 eligible individuals in LALES, 6357 (82%) had a clinical examination. One thousand two hundred sixty-three participants had definite diabetes and 1187 Latinos had T2DM. Of those with T2DM, 46% (544) had DR. Stepwise logistic regression analyses revealed that compared with females, males had a 50% higher risk of having any DR (OR = 1.50; $P = 0.006$). Factors independently associated with a greater risk of having any DR were longer duration of known diabetes (per year, OR = 1.08, $P < 0.0001$), higher glycosylated hemoglobin levels (per 1%, OR = 1.22, $P < 0.0001$); higher systolic blood pressure (per 20 mmHg, OR = 1.26, $P = 0.002$); and insulin treatment (OR = 1.60, $P = 0.01$). Factors independently associated with PDR included longer duration of known diabetes (per year, OR = 1.06, $P < 0.0001$); being on insulin treatment (OR = 3.2, $P < 0.0001$); and a higher systolic blood pressure (per 20 mmHg, OR = 1.44, $P = 0.01$). The relationship of these variables to the risk of having DR or PDR is not a constant linear function in all cases and varies depending on the variable.

Conclusions: Our study showed that the high risk of DR in adult Latinos is independently associated with both nonmodifiable and modifiable risk factors. These findings suggest that controlling hyperglycemia and hypertension in this ethnic group may reduce the high risk of having DR associated with T2DM. *Ophthalmology* 2007;114:1332–1340 © 2007 by the American Academy of Ophthalmology.

Type 2 diabetes mellitus (T2DM) has become one of the main public health challenges, especially because the associated macrovascular and microvascular complications result in significant morbidity and mortality, including cardiovascular disease, chronic renal disease, peripheral neuropathy, and visual impairment and blindness.¹ Com-

pared with African Americans and non-Hispanic whites, Latinos have a higher prevalence of diabetes mellitus (DM) and its complications.² Diabetic retinopathy (DR), in particular, is a leading cause of low vision and blindness in Latinos in the United States and several reports have found it to be more prevalent in Latinos than in most other ethnic groups.^{2–4} Recently, we have also reported

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on the high prevalence of DR in Latinos and found that DR was a common cause of low vision and blindness among Latinos.^{4,5}

Three population-based studies from San Antonio,⁶ San Luis Valley,⁷ and Arizona⁸ have evaluated risk factors associated with the presence of DR in Latinos. However, the San Antonio and San Luis Valley studies had small numbers of Latinos with DR ($n = 115$ and $n = 71$, respectively), and neither provided information describing risk relationships for Latinos alone.^{6,7} Information was also available from Latinos participating in the Proyecto VER study.⁸ The authors reported older age, male gender, longer duration of T2DM, higher glycosylated hemoglobin, and insulin use to be associated with DR.⁸ Systemic blood pressure was not studied as a risk factor in that study.⁸ Thus, duration of T2DM and uncontrolled glycemia have been consistently identified as risk factors for DR. The purpose of this report is to examine the relationship between risk factors and the prevalence of DR in adult Latinos 40 years or older participating in the population-based Los Angeles Latino Eye Study (LALES).

Although there are many variables related to the risk of having and developing DR,⁹ including psychosocial ones, personal health practices, health care access, and utilization factors (Fig 1), in this report we focus on the relationships between various biologic risk factors and DR in a cohort of Latinos of primarily Mexican American ancestry diagnosed with T2DM. We also compare these risk relationships with those identified in previous studies in these and other racial/ethnic groups.

Materials and Methods

Design

The LALES was conducted on self-identified Latinos (primarily Mexican American), ages ≥ 40 years, living in the city of La Puente, California. The University of Southern California's Institutional Review Board approved the study, and all procedures were in accord with the standards of the Declaration of Helsinki for research involving human subjects. Informed consent was obtained from all study participants. Details of the study design, sampling plan, and baseline data are reported elsewhere.¹⁰ An in-home

questionnaire and a complete clinical and eye examination were administered to all eligible participants. Procedures pertinent to these analyses are presented below.

Determination of Diabetes Mellitus and Diabetic Retinopathy

Participants were asked about previous diagnoses of DM, and, if diagnosed, they were asked about their treatment regimen (oral hypoglycemic medications, insulin, or diet alone). As part of the examination, random blood glucose and glycosylated hemoglobin were measured using the Hemocue B-Glucose Analyzer (Hemocue Inc., Lake Forest, CA) and the DCA 2000+ System (Bayer Corporation, Tarrytown, NY), respectively. Participants were diagnosed with having definite DM if on examination they had a history of diabetes and were being treated with oral hypoglycemic medications, insulin, or diet alone; their glycosylated hemoglobin was $\geq 7.0\%$, or if their random blood glucose level was ≥ 200 mg%. All definite cases of diabetes were considered to be T2DM if their age at diagnosis was ≥ 30 years. If their DM was diagnosed before the age of 30 and was being treated with insulin it was considered to be type 1 DM. Duration of diabetes was calculated as the difference between the year of diagnosis (as reported by the participant) and the year of the LALES examination.

A series of detailed photographs of the fundus was obtained in those individuals identified as having DM. Seven standard fields of the fundus for each eye were obtained using the Topcon TRC 50EX Retinal Camera (Topcon Corporation of America, Paramus, NJ) using Ektachrome 100 film (Kodak, Rochester, NY). Complete details of these 7 standard fields are detailed elsewhere.¹¹ The Ocular Epidemiology Grading Center at the University of Wisconsin, Madison, graded the stereoscopic fundus photographs in a masked manner. Diabetic retinopathy was defined as retinopathy in persons with definite DM. Grading protocols for DR are modifications of the Early Treatment Diabetic Retinopathy Study adaptation of the modified Airlie House classification of DR.¹¹ Eyes were graded using a 21-step scale (levels 10, 12, 13, 14, 15, 20, 31, 37, 43, 47, 53, 60, 61, 62, 63, 64, 65, 71, 75, 81, 85). A more detailed discussion of this grading method has been described previously.⁴ The retinopathy level for a participant is derived by giving the eye with the higher level greater weight. For purposes of this analysis retinopathy was defined as follows: (1) no DR (levels 10–13); (2) any DR (levels 14–85); or (3) a nonproliferative DR (NPDR) (mild [level 14–20], moderate [levels 31–43], or severe [levels 47–53] or proliferative DR [PDR; levels 60–85]).

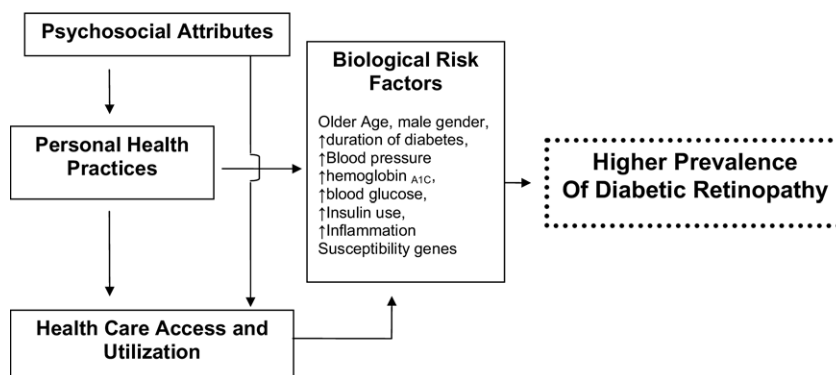


Figure 1. A modified conceptual model highlighting the relationship of biologic risk factors, psychosocial attributes, personal health practices, and health care access and utilization and diabetic retinopathy. ↑, higher level of the variable. Modified from Varma.⁹

Table 1. Univariate Associations with Any Diabetic Retinopathy

Risk Factors	Any Diabetic Retinopathy				P Value*	Selected Covariates [†]
	None (n = 643)		Yes (n = 544)			
	n	(%)	n	(%)		
Demographic factors						
Age group (yrs)						
Mean (\pm SD)	643	57.7 (10.5)	544	59.5 (10.1)	0.003	
40–49 (index)	160	24.9	102	18.8	0.02	
50–59	216	33.6	178	32.7		X
60–69	172	26.8	159	29.2		
70–79	77	12.0	93	17.1		
\geq 80	18	2.8	12	2.2		
Gender					0.06	
Female (index)	375	58.3	288	52.9		X
Male	268	41.7	256	47.1		
Country of birth					0.09	
U.S. (index)	181	28.2	173	31.8		
Mexico	397	61.8	334	61.4		X
Other	64	10.0	37	6.8		
Native American ancestry					0.46	
No (index)	604	94.1	506	93.0		
Yes	38	5.9	38	7.0		
Clinical and ocular factors						
Body mass index					0.0004	
<25 kg/m ² (index)	39	6.1	52	9.9		X
Overweight (25–29.9 kg/m ²)	192	30.2	196	37.5		
Obese (\geq 30.0 kg/m ²)	404	63.6	275	52.6		
Waist/hip ratio						
Index = low/normal (men)	74	27.8	67	26.7	0.77	
High: men>0.95	192	72.2	184	73.3		
Index = low/normal (women)	19	5.2	8	2.8	0.13	
High: women>0.8	349	94.8	277	97.2		
Known duration of diabetes (yrs)						
Mean (\pm SD)	452	6.8 (7.8)	486	12.5 (9.2)	<0.001	X
Newly diagnosed (index)	190	29.6	58	10.7	<0.0001	
1–4	237	36.9	90	16.5		
5–9	97	15.1	124	22.8		
10–14	71	11.1	106	19.5		
\geq 15	47	7.3	166	30.5		
Random serum blood glucose level (mg%)						
Mean (\pm SD)	641	184.6 (86.9)	542	213.8 (92.0)	<0.0001	
<140 (index)	249	38.7	139	25.0	<0.0001	X
140–200	163	25.4	128	23.5		
>200	231	35.9	277	50.9		
Glycosylated hemoglobin						
Mean (\pm SD)	641	8.1 (1.9)	540	8.8 (2.0)	<0.0001	X
<6.5% (index)	127	19.8	63	11.6	<0.0001	
6.5%–10%	399	62.1	336	61.8		
>10.0%	117	18.2	145	26.7		
Blood pressure (mmHg)						
Systolic						
Mean (\pm SD)	642	127.9 (19.0)	541	132.7 (20.7)	<0.0001	X
>140	154	24.0	172	31.8	0.003	
Diastolic						
Mean (\pm SD)	642	76.2 (10.6)	541	75.6 (11.9)	0.34	
>90	59	9.2	67	12.4	0.08	X
Hypoglycemic treatment						
No insulin (index)	577	89.7	406	74.6	<0.0001	X
Insulin	66	10.3	138	25.4		
Cataract surgery (index = none)						
IOL either eye	28	4.4	50	9.2	0.001	X
IOL both eyes	18	2.8	34	6.3	0.004	X
Aphakia either eye	3	0.5	2	0.4	0.80	
Aphakia both eyes	0	0.0	0	0.0		
Refractive error—left eye (spherical equivalent)					0.08	
<–3.0 diopters	52	8.9	24	4.4		
–3.0 to 0.50 diopters	113	17.6	107	19.7		
–0.5 to +0.5 diopters (index)	242	37.6	219	40.3		X
+0.5 to +3.0 diopters	211	32.8	168	30.9		
>3.0 diopters	25	3.9	26	4.8		

IOL = intraocular lens; NA = not applicable; SD = standard deviation.

*Chi-square procedures.

[†] $P \leq 0.1$ entered in the multivariate logistic regression model.

Risk Factor Assessment

Candidate risk factors for our analyses of DR included demographic, clinical, and ocular factors. The in-home questionnaire provided the following demographic information: gender, age, country of birth, and Native American ancestry. During the in-home interview, the following clinical history information was obtained from the participant: previous diagnosis of diabetes, treatment of diabetes, age when diagnosed, and ocular disease history.

Risk factors were also obtained from the clinical examination, including weight, height, waist and hip circumference, random blood glucose level (using the Hemocue B-Glucose Analyzer), glycosylated hemoglobin (used the DCA 2000+ System), and systemic blood pressure. Two consecutive measurements of systolic and diastolic blood pressure were obtained using the random zero sphygmomanometer. Before measurements for weight, height, and waist and hip circumference were taken, the participant was asked to remove excess clothing, pocket items, and shoes. The participant was asked to stand straight and tall on the scale platform. The height lever was placed touching the crown of the participant's head, and measurements were read to the nearest 0.5 cm. Weight was measured to the nearest 0.1 kg (Detecto Scale, Webb City, MO). A nonstretchable tape measure was used to measure waist and hip circumference. Waist circumference was measured at the smallest area below the rib cage and above the umbilicus. Hip circumference was measured at the level of the largest extension of the buttocks. The waist-to-hip ratio for each participant was calculated by dividing the waist measurement by the hip measurement. Body mass index was defined as weight (in kilograms) divided by the square of the height in meters (kg/m^2). Body mass index categories were defined as underweight ($<18.5 \text{ kg}/\text{m}^2$), normal weight ($18.5\text{--}24.9 \text{ kg}/\text{m}^2$), overweight ($25.0\text{--}29.9 \text{ kg}/\text{m}^2$) and obese ($\geq 30.0 \text{ kg}/\text{m}^2$). Native American ancestry was attributed to any individuals who self-identified as being of American Indian or Alaskan native descent, or who identified their parents or grandparents as being of Native American descent.

In addition to an assessment of DR, the eye examination included an assessment of prior cataract surgery and measurements of noncycloplegic refractive error.

Statistical Analysis

Frequency distributions and chi-square analyses were conducted to assess the univariate association of risk factors with any DR (any DR vs. no DR), and with PDR and NPDR (PDR vs. NPDR). Risk factors with a P value ≤ 0.1 were considered as candidate risk factors for the stepwise multivariable logistic regression model. To identify and validate independent risk factors, forward and backward procedures were conducted, in which the risk factors were included in the model if the P value was < 0.05 . All analyses were performed using the Statistical Analysis System (version 9.0, SAS Institute Inc, Cary, NC).

In addition to estimating odds ratios for the independent risk factors for DR and PDR, we also modeled the nature of the relationship between various significant risk factors and DR. The predicted (estimated) probabilities of having any DR (or PDR) were obtained using the final model identified from the stepwise logistic regression procedure—after adjusting for the significant covariates. The estimated prevalences were plotted against the variables of interest (e.g., systolic blood pressure) and a locally weighted regression line was fitted using S-PLUS (Insightful Corporation, Seattle, WA).

Results

Of the 6357 eligible participants who completed a clinical examination, 1263 participants had definite DM; 1187 subjects (94% of those with definite DM) were identified as having T2DM. Almost half ($n = 544$, 46%) of those with T2DM had DR. Among those who were diagnosed with any DR, 168 (31%) had mild NPDR, 309 (57%) had moderate to severe NPDR, and 67 (12%) had PDR.

Table 1 shows the univariate associations of various risk factors with any DR. Candidate risk factors (those with $P < 0.10$) for the multivariable analyses are noted in the last column of the table. Older age, male gender, being born in the United States, not being obese, longer duration of diabetes, higher blood glucose levels, higher HbA_{1c} levels, insulin use, higher systolic and diastolic blood pressure, previous cataract surgery, and more hyperopic spherical equivalent refractive error were associated with having any DR and included in the multivariable model. Univariate associations between candidate risk factors and PDR (Table 2) included not being obese, longer duration of diabetes, higher systolic blood pressure, insulin use, and previous cataract surgery ($P < 0.10$).

Table 3 presents the results of the stepwise logistic regression analyses. The dependent variable was any DR; the independent variables were all candidate risk factors associated with any DR in Table 1. The biologic risk factors independently associated with the risk of having any DR in order of importance were longer duration of diabetes, elevated glycosylated hemoglobin, elevated systolic blood pressure, male gender, and treatment with insulin. When assessing the risk of having PDR compared with those participants who had NPDR, the independent factors associated with having PDR were longer duration of diabetes, insulin use, and higher systolic blood pressure (Table 4). Logistic regression analyses were also conducted using a backward procedure. All candidate risk factors were entered into the model and eliminated based on lack of significance. Results similar to those found using the forward and stepwise procedure were obtained.

On average, each year of longer duration of diabetes was associated with an 8% higher risk of having any DR. However, when the predicted probability of having any DR was plotted against duration of diabetes, 3 plateaus of prevalence were evident (Fig 2). These 3 suggest a DR prevalence of 20% to 30% in Latinos with T2DM for 0 to 4 years, a prevalence of 50% to 60% in those with T2DM for 5 to 14 years, and a prevalence of 75% to 95% in those with a T2DM duration of ≥ 15 years. In contrast, the relationship between the predicted prevalence of PDR and duration is linear, with the slope becoming steeper after duration of ≥ 20 years (Fig 3).

The relationship of level of glycosylated hemoglobin to estimated prevalence of any DR appears to be linear, with a suggestion of a plateau of the curve at $\geq 11\%$ (Fig 4). On average, there was a 22% higher prevalence of DR associated with every 1% higher level of glycosylated hemoglobin. Glycosylated hemoglobin was not independently associated with PDR.

Systolic blood pressure also appears to be linearly related to both the estimated prevalence of any DR and PDR (Figs 5, 6). However, although the slope for any DR and systolic blood pressure is constant over the 90 to 170 mmHg range, the relationship with PDR is not constant, and the slope is steeper at blood pressures of ≥ 150 mmHg. This suggests that there is a higher risk of having PDR in persons with systolic blood pressures of ≥ 150 mmHg compared with those with lower systolic blood pressures.

Table 2. Univariate Associations with Proliferative (PDR) and Nonproliferative Diabetic Retinopathy (NPDR)

Risk Factors	DR				P Value*
	NPDR (n = 477)		PDR (n = 67)		
	n	(%)	n	(%)	
Demographic					
Age (yrs)					
Mean (\pm SD)	477	59.3 (10.1)	67	61.2 (9.8)	0.16
40–49 (index)	93	19.5	9	13.4	0.34
50–59	160	33.5	18	26.9	
60–69	134	28.1	25	37.3	
70–79	79	16.6	14	20.9	
\geq 80	11	2.3	1	1.5	
Gender					
Female (index)	248	52.0	40	59.7	0.24
Male	229	48.0	27	40.3	
Country of birth					
U.S. (index)	151	31.7	22	32.8	0.71
Mexico	295	61.8	39	58.2	
Other	31	6.5	6	8.9	
Native American ancestry					
No (index)	446	93.5	60	89.6	0.24
Yes	31	6.5	7	10.5	
Clinical and ocular					
Body mass index					
< 25 kg/m ² (index)	42	9.1	10	15.9	0.08
Overweight (25–29.9 kg/m ²)	169	36.7	27	42.9	
Obese (\geq 30.0 kg/m ²)	249	54.1	26	41.3	
Waist/hip ratio					
Index = low/normal (men)	59	26.2	8	30.8	0.62
High: men >0.95	166	73.8	18	69.2	
Index = low/normal (women)	8	3.3	0	0.0	0.25
High: women >0.8	237	96.7	40	100.0	
Random blood glucose level (mg%)					
Mean (\pm SD)	475	215.2 (93.6)	67	203.3 (79.9)	0.32
<140 (index)	122	25.6	17	25.4	0.99
140–200	112	23.5	16	23.9	
>200	243	50.9	34	50.8	
Duration of diabetes (yrs)					
Mean (\pm SD)	421	11.7 (8.6)	65	18.0 (10.6)	<0.0001
Newly diagnosed (index)	56	11.7	2	3.0	<0.0001
1–4	87	18.2	3	4.5	
5–9	113	23.7	11	16.4	
10–14	92	19.3	14	20.9	
\geq 15	129	27.0	37	55.2	
Glycosylated hemoglobin					
Mean (\pm SD) %	473	8.9 (2.0)	67	8.5 (2.0)	0.19
<6.5% (index)	53	11.1	10	14.9	0.19
6.5%–10%	291	61.0	45	67.2	
>10.0%	133	27.9	12	17.9	
Blood pressure (mmHg)					
Systolic					
Mean (\pm SD)	474	131.8 (20.4)	67	139.6 (21.3)	0.004
>140	143	30.2	29	43.3	0.03
Diastolic					
Mean (\pm SD)	474	75.4 (11.8)	67	76.7 (12.7)	0.42
>90	56	11.8	11	16.4	0.28
Hypoglycemic treatment					
No insulin (index)	373	78.2	33	49.3	<0.0001
Insulin	104	21.8	34	50.8	
Cataract surgery (index = none)					
IOL either eye	35	7.4	15	22.4	<0.0001
IOL both eyes	26	5.5	8	11.9	0.04
Aphakia either eye	1	0.2	1	1.5	0.11
Aphakia both eyes	0	0.0	0	0.0	NA
Refractive error left eye (spherical equivalent)					
<–3.0 diopters (index)	21	4.4	3	4.5	0.35
–3.0 to 0.50 diopters	88	18.5	19	28.4	
–0.5 to +0.5 diopters	198	41.5	21	31.3	
+0.5 to +3.0 diopters	147	30.8	21	31.3	
>3.0 diopters	23	4.8	3	4.5	

IOL = intraocular lens; SD = standard deviation.

*Chi-square procedures.

Table 3. Stepwise Multivariate Model of Diabetic Retinopathy

Risk Factor	Step in Selection	Any DR vs. No DR	
		OR (95% CI)	P Value*
Diabetes duration (per year)	1	1.08 (1.06–1.11)	<0.0001
Glycosylated hemoglobin (per 1%)	2	1.22 (1.13–1.31)	<0.0001
Systolic blood pressure (per 20 mmHg)	3	1.26 (1.08–1.47)	0.002
Gender			
Female (index)	4	1.00	0.006
Male		1.50 (1.13–2.01)	
Hypoglycemic treatment			
No insulin (index)	5	1.00	0.01
Insulin use		1.60 (1.12–2.30)	

CI = confidence interval; DR = diabetic retinopathy; OR = odds ratio.
 Variables included in the multivariate model are age, gender, country of birth, body mass index, duration of diabetes, cataract surgery, refractive error, random blood glucose, diastolic and systolic blood pressure, glycosylated hemoglobin, and insulin use.
 *Stepwise logistic regression procedures.

Discussion

We identified male gender, longer duration of T2DM, elevated glycosylated hemoglobin, higher systolic blood pressure, and treatment with insulin to be independently associated with any DR. In addition, longer duration of T2DM, higher systolic blood pressure, and insulin use were also risk factors for having PDR. We also demonstrated that the relationship of these variables to the risk of having DR or PDR is not a constant linear function in all cases and varies depending on the variable of interest and the disease outcome. For example, although there may be various thresholds for duration of T2DM and the risk of having any DR, the relationship of duration with PDR appears to be linear. Similarly, there is a constant linear relationship between systolic blood pressure and any DR; the risk of having PDR varies depending on the level of systolic blood pressure—the risk of having PDR is higher when systolic blood pressure is approximately ≥ 150 mmHg compared with lower levels of systolic blood pressure. Finally, the relationship of glycosylated hemoglobin and any DR appears to be higher at moderately high levels (11%) and then appears to reach a threshold at the highest levels of glycosylated hemoglobin. In contrast, glycosylated hemoglobin was not independently associated with PDR in our study. These

differences in the relationships between risk factors and outcomes may provide some insight into the mechanisms of DR and PDR.

In our study, duration of T2DM was the most important risk factor for both any DR and PDR. In the stepwise selection of variables, in the models for any DR and PDR, it was the first variable entered into the model, highlighting its primary importance in the risk of having any DR and PDR. This has also been shown in other studies on Latinos and persons of African and European ancestry.^{2–4,6–8,12} Duration of T2DM has been hypothesized as a surrogate for the magnitude of exposure to hyperglycemia and other risk factors. In our data, the thresholds of prevalence of DR with regard to duration of disease suggest that the risk of having DR is not linearly associated with exposure to various risk factors, but the risk relationship may be cumulative, such that the risk of having DR “jumps higher” after certain periods of exposure. This is consistent with data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) in persons diagnosed with DM after 30 years of age.¹² In that study, a nonlinear relationship between duration of DM and prevalence of DR was found with 3 increasing levels of prevalence between 0 and 5 years, 6 and 15 years, and >15 years duration. For PDR, the relationship with duration of T2DM appears to be more linear, with the risk of having PDR becoming higher after 20 years of duration of

Table 4. Stepwise Multivariate Model of Proliferative Diabetic Retinopathy (PDR) versus Nonproliferative Diabetic Retinopathy (NPDR)

Risk Factor	Step in Selection	PDR vs. NPDR	
		OR (95% CI)	P Value*
Diabetes duration (per year)	1	1.06 (1.03–1.09)	<0.0001
Hypoglycemic treatment	2		
No insulin (index)		1.00	
Insulin use		3.2 (1.79–5.69)	<0.0001
Systolic blood pressure (per 20 mmHg)	3	1.44 (1.09–1.89)	0.01

CI = confidence interval; OR = odds ratio.
 Variables included in the model are age, body mass index, cataract surgery glycosylated hemoglobin, systolic and diastolic blood pressure, insulin use, and diabetes duration.
 *Stepwise logistic regression procedures.

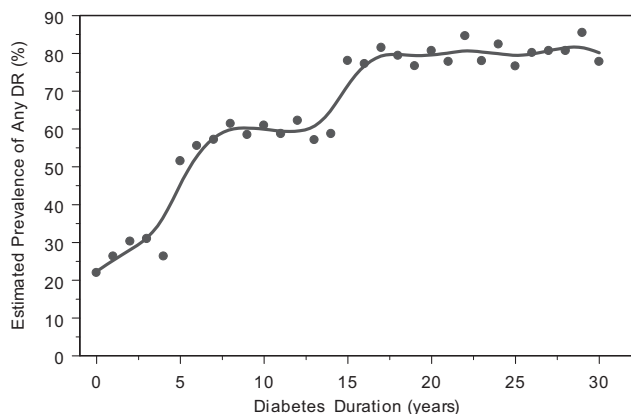


Figure 2. Diabetes duration-specific estimated prevalence of any diabetic retinopathy (DR) with the locally weighted regression line for all participants with type 2 diabetes mellitus in the Los Angeles Latino Eye Study. The estimated prevalence of having any DR was obtained using the final model identified from the stepwise logistic regression procedure. The duration-specific data of all persons by each year of duration were plotted to show the independent relationship of known duration of diabetes mellitus with DR prevalence.

T2DM. This relationship again is similar to data from WESDR, where ≥ 15 years duration of DM was associated with an increase in the frequency of PDR.¹² These data provide some general guidance to clinicians that although the risk of having DR is low in persons with < 5 years duration of T2DM, the risk is significantly higher in those persons with longer duration of T2DM. More important, from a vision-threatening standpoint, the risk of having PDR is significantly higher in those with duration of T2DM of ≥ 15 years. However, an important caveat to this is that even though the risk of having DR and PDR is greater in persons with longer duration of disease, there is a smaller but significant risk of having DR and PDR even in persons with newly diagnosed T2DM or in persons with shorter duration of T2DM. Because aggressive management of DR and PDR can prevent vision loss, all

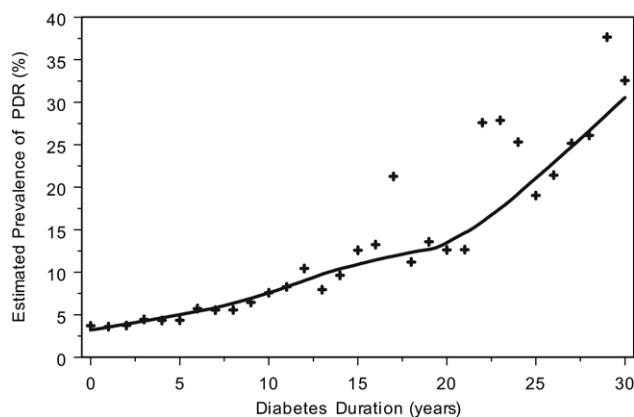


Figure 3. Diabetes duration-specific estimated prevalence of proliferative diabetic retinopathy (PDR) with the locally weighted regression line for all participants with type 2 diabetes mellitus in the Los Angeles Latino Eye Study. The duration-specific data of all persons by each year of duration were plotted to show the independent relationship of known duration of diabetes mellitus with PDR prevalence.

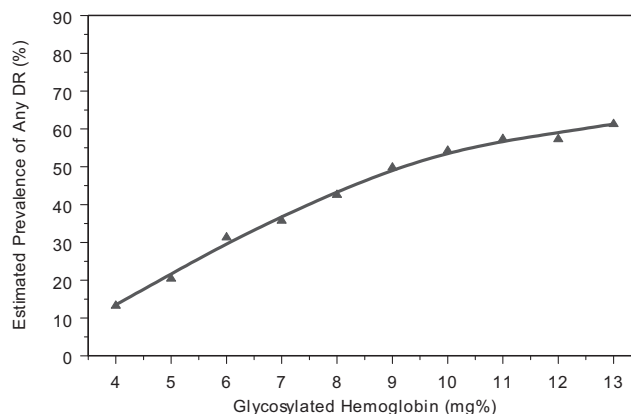


Figure 4. Estimated prevalence of any diabetic retinopathy (DR) by glycosylated hemoglobin levels with the locally weighted regression line for all participants with type 2 diabetes mellitus in the Los Angeles Latino Eye Study. The glycemia-specific prevalence data of all persons by each 1% difference in the level of glycemia were plotted to show the independent relationship of glycemia with DR prevalence.

persons with T2DM should be referred for a comprehensive eye examination to detect, prevent, and manage visual loss and blindness from DR.

Poor glycemic control and insulin use were also important risk factors for the presence of any DR when compared with persons with no DR. Insulin use is considered to be a surrogate measure of poor previous glycemic control, as insulin is generally indicated in persons with T2DM when hyperglycemia cannot be controlled with both lifestyle modification (exercise and dietary modification) and oral hypoglycemic agents. Poor glycemic control has also been identified as an important risk factor in other cross-sectional and longitudinal cohort studies and in clinical trials.^{6-8,12-17} The underlying pathogenic hypothesis is that hyperglycemia causes an accumulation of sorbitol and advanced glycation end products, activation of the β and δ isoforms of protein

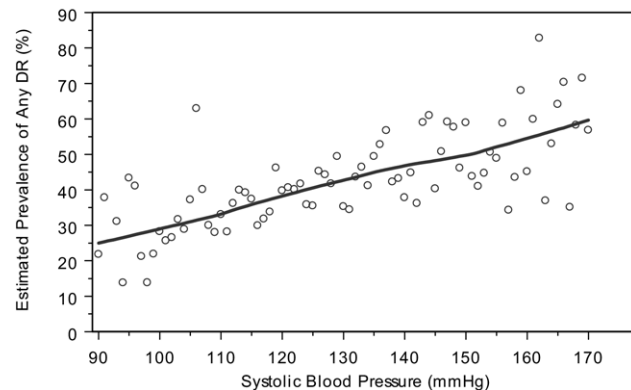


Figure 5. Estimated prevalence of any diabetic retinopathy (DR) by systolic blood pressure with the locally weighted regression line for all participants with type 2 diabetes mellitus in the Los Angeles Latino Eye Study. The blood pressure-specific prevalence data of all persons by each 10 mmHg difference in the level of systolic blood pressure were plotted to show the independent relationship of systolic blood pressure with DR prevalence.

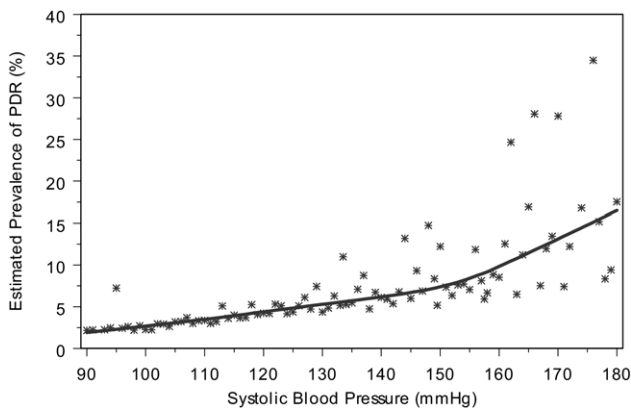


Figure 6. Estimated prevalence of proliferative diabetic retinopathy (PDR) by systolic blood pressure with the locally weighted regression line for all participants with type 2 diabetes mellitus in the Los Angeles Latino Eye Study. The blood pressure-specific prevalence data of all persons by each 10 mmHg difference in the level of systolic blood pressure were plotted to show the independent relationship of systolic blood pressure with PDR prevalence.

kinase C, increased oxidative stress, and the production of angiogenic factors (such as vascular endothelial growth factor and pigment endothelium-derived growth factor) in the retina and retinal microvasculature. These then lead to endothelial dysfunction and the development of retinopathy. Data from Wisconsin, Arizona, and the United Kingdom Prospective Diabetes Study have shown that better glycemic control results in a decreased incidence and progression of DR in persons with T2DM.^{14–17}

Although we were unable to find an independent relationship between PDR and glycosylated hemoglobin, there was a significant independent relationship between insulin use and PDR when compared to persons with NPDR. In the Proyecto VER study of Latinos from Arizona, no independent relationship between PDR and glycemic control was present, but there was a significant independent relationship between insulin use and PDR.⁸ Conversely, longitudinal studies have demonstrated a strong relationship between glycosylated hemoglobin levels and incidence and progression of PDR.^{14–17} This may be due to the design limitation of cross-sectional studies such as LALES and Proyecto VER, in assessing antecedent-consequent relationships between glycemic control and PDR. Because intensive insulin treatment in persons with T2DM and poor glycemic control may prevent the progression of diabetic microvascular complications,¹⁸ it is likely that persons with these complications (e.g., PDR) may be more likely to be treated with insulin than those without these complications. The relation of glycemic control and the risk of having PDR in Latinos will require longitudinal observation of the cohort to be informative.

Systolic blood pressure was found to be associated with having both DR and PDR.^{19,20} It is hypothesized that hyperglycemia disrupts retinal microvascular autoregulation and makes the endothelium of the small blood vessels more susceptible to damage by high blood pressure.²¹ In this setting, elevated blood pressure (and retinal hyperperfusion) lead to capillary injury, retinal nonperfusion, and the development or

progression of retinopathy.¹⁹ There have been conflicting results from other population-based studies. Although there was a higher risk of having DR with higher systolic blood pressure in the San Luis Valley study, no relationship was found in the San Antonio study.^{6,7} Blood pressure was not evaluated as a risk factor in the Proyecto VER study.⁸ In WESDR, blood pressure was not found to be associated with either incidence or progression of DR or PDR in persons with older-onset DM (presumably T2DM), possibly due to selective survival.²² Two clinical trials have evaluated the impact of lowering systemic blood pressure on the progression of retinopathy in T2DM.^{23,24} In the UK Prospective Diabetes Study, a tighter control of blood pressure was associated with a 34% reduction in the progression of retinopathy.²³ On the other hand, in the Appropriate Blood Pressure Control in Diabetes trial, no difference in the rates of progression of DR was found between the intensive blood pressure control and the moderate blood pressure control groups.²⁴ Thus, although there is a suggestion of an independent beneficial effect of lower blood pressure on the risk of having and developing retinopathy in persons with T2DM, further evidence is needed to unequivocally demonstrate the value of aggressive systemic hypotensive therapy in decreasing the incidence and progression of DR.

Finally, men in our study had a 50% higher risk of having any DR compared with women. However, gender was not related to prevalent PDR. These results are similar to those in the Proyecto VER study, in which men had a 61% higher risk of having any DR but were not at higher risk of having PDR when compared with women.⁸ However, neither the San Luis Valley study nor the San Antonio study noted a higher risk of having DR in Latino men compared with women.^{6,7} Also, in WESDR, men with older-onset DM did not have a higher incidence or progression of DR or PDR.¹⁴ The reason for this higher risk in Latino males in our study and in the Proyecto VER study remains unclear, particularly because no interactions with other biologic variables were identified. Thus, when we explored the relationship of various other risk factors with gender, we found no significant associations. This higher risk in Latino men needs to be validated and elucidated in longitudinal studies.

Our study has several strengths and limitations. First, it is one of the largest population-based studies of risk factors for DR in Latinos with T2DM. The LALES sample is similar in age distribution to Latinos of Mexican origin in the United States; therefore, our data are applicable to other Latinos of Mexican origin in the United States. Second, we used standardized protocols for obtaining stereoscopic photographs of the 7 Early Treatment Diabetic Retinopathy Study fields and for grading DR. A limitation to our study in assessing risk factors is that the cross-sectional design of our study considers only the type and magnitude of risk factors at the time of data collection without taking any temporal trends and relationships into account. Thus, we do not have multiple regular assessments of systemic blood pressure, glycosylated hemoglobin, or insulin use to provide a clearer temporal relationship between these risk factors and the development of DR or PDR. Second, if persons with DR or PDR and the presence of risk factors (e.g., poorer glycemic control and PDR) were less likely to survive, then our data could have a survivor bias. However, this differential survival would only underestimate the relation-

ship between a risk factor and its association with DR or PDR. Thus, our data may provide an underestimate of the risk relationships. Finally, there is the likelihood of uncontrolled confounding. We did not assess other biologic variables such as antioxidant levels, inflammatory markers, and genetic markers. These markers could potentially modify the relationships between the risk factors studied and the risk of having DR or PDR.

In summary, our population-based study of primarily Mexican American Latinos with T2DM provides some insight into the relationship between biologic risk factors and the risk of having DR and PDR. These relationships are particularly important because interventions aimed at these risk factors can potentially lower the morbidity associated with DR and PDR. The public health value of intervention programs to lower the risk of having chronic microvascular complications such as DR or PDR becomes more urgent as the incidence of T2DM, especially in the fastest growing segment of the American population, increases, coupled with an increase in the life expectancy.

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Appendix: The Los Angeles Latino Eye Study Group

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