Diabetic Retinopathy in Oklahoma Indians With NIDDM

Incidence and risk factors

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OBJECTIVE — To determine the incidence rates and risk factors for development of diabetic retinopathy in Oklahoma Indians.

RESEARCH DESIGN AND METHODS — Cohort follow-up study with baseline examination between 1972 and 1980 and follow-up examination between 1987 and 1991. Mean ± SD follow-up time was 12.8 ± 1.7 yr. Eleven Indian Health Service facilities (clinics and hospitals) in Oklahoma participated in the study. Study participants were a quasirandom sample of 1012 American Indians (379 men, 633 women) in Oklahoma with NIDDM, 927 of whom received a detailed eye examination at baseline. The mean age of participants was 52 yr with a duration of diabetes of 6.9 yr at baseline. The average quantum of Indian blood was 92% (77% full blood). At follow-up, 515 (55.6%) were alive, 408 (44.0%) were deceased, and 4 (0.4%) could not be traced. Of the living participants, 380 (73.8%) underwent an ophthalmoscopic examination.

RESULTS — The incidence of retinopathy among the participants who were free of disease at baseline and who survived the follow-up interval was 72.3%. By multivariate analysis, significant independent predictors of retinopathy recorded at baseline were FPG level, therapeutic regimen, systolic blood pressure, and duration of diabetes. FPG levels ≥11.1 mM (200 mg/dl) increased the risk of retinopathy 1.7 times that for levels <7.8 mM (140 mg/dl). Insulin use was associated with a 20% greater incidence. Hypertension was a particularly significant risk factor for those with lower FPG levels.

CONCLUSIONS — Given that NIDDM is reaching epidemic proportions in Oklahoma Indians and that most may be afflicted with retinopathy, frequent ophthalmological examinations are clearly indicated for this high-risk population. The role of intervention, namely glycemic and hypertensive control, deserves further study.

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NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; FPG, FASTING PLASMA GLUCOSE; BMI, BODY MASS INDEX; RR, RELATIVE RISK; CI, CONFIDENCE INTERVAL.

Diabetic retinopathy is one of the leading causes of visual impairment and blindness in the U.S., resulting in an estimated public welfare expense and lost income of more than $75 million annually (1,2). Based on 1987 estimates, ~5.8 million people have been diagnosed with diabetes (3); 90–95% of whom have ketosis-resistant NIDDM (4). Among the >5 million people with NIDDM in the U.S., up to 80% will develop diabetic retinopathy within 20 yr of diagnosis of diabetes (5–7). For Oklahoma Indians, NIDDM has risen from apparent rarity before 1940 to affect ~33% of adults >30 yr old in the 1970s (8). It is believed that the NIDDM rate in Oklahoma Indians is comparable to that in other American Indians (9). American Indians with NIDDM appear to suffer from the same manifestations and vascular complications as non-Indians (10). NIDDM is considered one of the most serious health problems in this population; ~50% of all deaths may be attributable to diabetes and its complications (11). As in the Pima Indians, insulin-dependent diabetes mellitus is believed to be rare among Oklahoma Indians, for unknown reasons (10,12).

In 1980, West et al. (15) reported the prevalence of diabetic retinopathy in a cohort of ~1000 diabetic Oklahoma Indians to be 24.4%. In their study, they identified risk factors associated with retinopathy to include the level of FPG, duration of diabetes, need for insulin therapy, level of plasma triglyceride, and younger age of onset of diabetes. In this study, we present the results of a follow-up study of these subjects, examined on average >12 yr later, to determine the cumulative incidence and risk factors for diabetic retinopathy among those who were initially free of disease. We compared our results for Oklahoma Indians with reports from other populations, including the general population and Pima Indians. The cumulative incidence and risk factors for proliferative

retinopathy in our cohort have been reported elsewhere (13).

RESEARCH DESIGN AND METHODS— Between 1972 and 1980, 1012 Oklahoma Indians with NIDDM were examined at the Indian Health Service facilities in Oklahoma, all of whom had FPG (*o*-toluidine method) ≥7.8 mM (140 mg/dl) or a 2-h postload plasma glucose level ≥11.1 mM (200 mg/dl). These patients were diagnosed as diabetic between 1937 and 1980 with a median duration of diabetes of 5 yr (25th percentile, 2 yr; 75th percentile, 10 yr) at initial examination. The mean ± SD age of the patients was 52.0 ± 11.3 yr. The baseline examination included a personal interview and physical examination. The personal interview was conducted by a trained registered nurse, and the examinations were conducted by Dr. Kelly West and associates (who were trained by him). All of the examiners followed the protocol of the World Health Organization Multinational Study of Vascular Disease in Diabetes (14). Recruitment methods and examination procedures have been described elsewhere (13,15).

Among these patients, 927 (571 women, 356 men) received a detailed eye examination by ophthalmoscopy through dilated pupils. Nonproliferative retinopathy was defined by the presence of one or more red lesions or soft exudates (16). Proliferative diabetic retinopathy was defined by the presence of neovascularization, vitreous hemorrhage, or any evidence of photocoagulation, presumably directed at new vessels (16). The term of any retinopathy refers to the nonproliferative or proliferative retinopathy.

Between 1988 and 1991, the original study subjects were asked to participate in a follow-up study. At follow-up, 515 (55.6%) were alive, 408 (44.0%) were dead, and 4 (0.4%) could not be traced. Among living participants, 448 (87.0%) participated in a personal interview and physical examination, and 380 (73.8%) were available for a complete ophthalmological examination by three ophthalmologists with special training in retinal diseases. The follow-up examination followed the baseline examination protocol. The average time of follow-up for the 380 patients was 12.8 ± 1.7 yr (range 10–17.7 yr).

Overall retinopathy level was defined by the more severely affected eye. The cumulative incidence of any retinopathy was estimated from all subjects who had no retinopathy at the baseline examination who participated in the follow-up examination (332 subjects). Several variables measured at baseline were assessed as risk factors for the development of any retinopathy. These included age, duration of diabetes, BMI (weight/height^2 [kg/m^2]), macrovascular disease (defined by the Rose and Blackburn questionnaire on angina and intermittent claudication, history of stroke, history of myocardial infarction, or evidence of ischemic heart disease by electrocardiogram), renal disease (defined by plasma creatinine >133 μM [1.5 mg/dl] or slight or heavy proteinuria by the salicylsulfonic acid test), treatment (insulin, oral agent, and diet alone), smoking status, and blood pressure (systolic and diastolic). Classification of hypertension required systolic blood pressure ≥160 mmHg, diastolic pressure ≥95 mmHg, or use of hypertensive medication.

For those patients who were not examined at follow-up, including those deceased, medical charts were reviewed for a diagnosis of retinopathy. Statistic methods used included the two-tailed Student's *t* test, the χ^2 statistic, and stepwise linear logistic regression to test associations between baseline variables and retinopathy outcomes (17–21).

RESULTS— Among the 927 subjects who participated in the baseline interview and physical examination, including ophthalmoscopic examination, 515 (55.6%) survived to the time of our follow-up study. Of these, 380 (73.8%) underwent an ophthalmoscopic examination at follow-up. Selected characteristics of participants and living nonparticipants (or lost to follow-up) were reviewed (Table 1). The nonparticipants who were alive at the time of follow-up did not differ significantly from the participants except that they were typically younger at the initial interview and younger at diagnosis.

Of the 380 participants who underwent follow-up ophthalmological examinations with fundus examination, there were 332 subjects who had no retinopathy at baseline examination. Of these 332, 240 (72.3%) developed retinopathy in the follow-up interval period. Six of 48 (12.5%) participants with retinopathy at baseline demonstrated improvement (Table 2).

To assess the reliability of medical records with respect to the diagnosis of retinopathy, medical charts of nonparticipants were also reviewed. Of the 408 deceased, 253 (62.0%) did not have retinopathy at the baseline examination. According to the chart review, 65 (25.7%) developed retinopathy. Of the 139 nonparticipants who were alive, 113 were at risk for developing retinopathy, 21 (18.6%) of whom had charts that noted the disease. We believe these results represent underestimates. When we reviewed the charts of 48 randomly selected participants in the study who had fundus examinations at follow-up, 0 of 8 with no retinopathy at follow-up had retinopathy mentioned in their charts (false-positive rate of 0). However, of the 40 who had retinopathy at follow-up, only 20 (50%) had retinopathy reported in the chart. The most likely explanation for this observation is that the patients did not routinely undergo eye examinations as part of their medical care.

To determine the influence of potential risk factors on the development and progression of diabetic retinopathy, univariate analysis was performed for patients who were free of the disease at baseline who participated in the follow-up study (332 subjects) (Table 3). Risk factors examined included the participant's age, sex, duration of diabetes,

Table 1—*Selected baseline variables of participants and nonparticipants*

	Participants	Nonparticipants (lost to follow-up)	*P*
n (M/F)	130/250 (34.2/65.8)	52/87 (37.4/62.6)	0.499
Age (yr)	48.2 ± 8.4	46.5 ± 8.2	0.046
Duration of NIDDM (yr)	5.2 ± 4.9	6.0 ± 5.0	0.096
Age at diagnosis (yr)	43.0 ± 9.2	40.6 ± 8.3	0.006
BMI (kg/m^2)	32.1 ± 5.9	33.3 ± 8.1	0.112
Smoking (*n*)			
No	228 (60.2)	81 (58.3)	0.698
Yes	151 (39.8)	58 (41.7)	
Blood pressure (mmHg)			
Systolic	131.8 ± 17.7	132.2 ± 17.1	0.818
Diastolic	83.7 ± 10.6	83.6 ± 12.0	0.922
FPG (mM)	10.2 ± 4.2	10.6 ± 4.1	0.503
Cholesterol (mM)	5.3 ± 1.6	5.4 ± 1.3	0.852
Triglycerides (mM)	24.9 ± 25.7	22.1 ± 13.6	0.114
Creatinine (μM)	79.8 ± 44.3	70.9 ± 26.6	0.815
Hypertension (*n*)			
No	256 (67.4)	91 (65.5)	0.684
Yes	124 (32.6)	48 (34.5)	
Renal Disease (*n*)			
No	296 (77.9)	109 (78.4)	0.899
Yes	84 (22.1)	30 (21.6)	
Macrovascular disease (*n*)			
No	240 (63.2)	85 (61.2)	0.676
Yes	140 (36.8)	54 (38.8)	
Therapeutic regimen (*n*)			
Diet	128 (34.1)	41 (29.7)	0.482
Oral agent	195 (52.0)	73 (52.9)	
Insulin	52 (13.9)	24 (17.4)	
Visual impairment (*n*)			
Blind	0	1 (0.7)	0.367
Mildly severe	48 (12.6)	16 (11.5)	
Normal	332 (87.4)	122 (87.8)	
Baseline retinopathy (*n*)			
None	332 (87.4)	113 (81.3)	0.081
Nonproliferative	44 (11.5)	26 (18.7)	
Proliferative	4 (1.1)	0	

Values are means ± SD. Percentages given in parentheses.

FPG, therapeutic regimen, systolic and diastolic blood pressure, hypertension status, BMI, plasma cholesterol, plasma triglyceride, smoking status, and presence of macrovascular or renal disease (as defined above), all recorded at baseline; and age at diagnosis.

Factors significantly associated with the risk of developing retinopathy were age, age at diagnosis, duration of diabetes, FPG, systolic and diastolic blood pressure and baseline therapeutic regimen. Other factors including sex, hypertension status, plasma cholesterol level, plasma triglyceride, BMI, smoking, and macrovascular and renal diseases were not significantly associated.

Table 2—*Status of eye disease at follow-up*

	At risk (*n*)	Cumulative incidence, *n* (%)
Any retinopathy	332	240 (72.3)
Proliferative retinopathy	376	58 (15.4)
No change	380	119 (31.1)
Improvement	48	6 (12.5)

The group means for those participants who did and did not develop any form of retinopathy were calculated for selected continuous variables; the Student's *t* test was performed to assess the likelihood that any differences observed were due to chance. The mean systolic blood pressure at baseline for those who developed retinopathy (133.1 mmHg) was significantly greater compared with those who remained free of retinopathy at follow-up (127.6 mmHg, $P < 0.008$). Similarly, the mean diastolic blood pressures for the two groups were significantly different ($P < 0.011$), namely 84.6 and 81.4 mmHg, for those who developed retinopathy and those free of retinopathy, respectively. Also, the mean plasma triglyceride levels at baseline of the two groups were 26.7 (236.6) and 20.6 mM (182.5 mg/dl), respectively, again significantly different ($P = 0.008$). The difference between baseline FPG levels of the two groups was striking. Those who developed retinopathy had an average level (10.8 mM [195.1 mg/dl]), which was ~3 mM (50 mg/dl) higher than those who remained free of disease (7.9 mM [142.6 mg/dl; $P < 0.0001$]). Those who developed retinopathy were also on average younger (48 vs. 50 yr, $P < 0.05$), were diagnosed with diabetes at a younger age (43 vs. 46 yr, $P < 0.002$), and had longer duration of diabetes (5.1 vs. 3.8 yr, $P < 0.013$). No significant difference was observed between the two groups in terms of BMI and plasma cholesterol level.

FPG, systolic and diastolic blood pressure, and initial therapeutic regimen remained significant predictors of the development of retinopathy when stratified by duration of diabetes (Fig. 1). In all groups, the highest incidence of retinopathy was found among those participants whose duration of diabetes at initial in-

Table 3—*Cumulative incidence rates of retinopathy by baseline variables*

	At risk (*N*)	Cumulative incidence, *N* (%)	*P*	Relative risk RR (95% CI)*
Sex				
Female	222	160 (72.1)	0.900	1.00
Male	110	80 (72.7)		1.01 (0.88–1.16)
Age (yr)				
<35	14	10 (71.4)		1.00
35–44	108	82 (75.9)	0.048	1.06 (0.75–1.50)
45–54	160	120 (75.0)		1.05 (0.74–1.48)
≥55	50	28 (56.0)		0.78 (0.52–1.18)
Age at diagnosis (yr)				
<35	55	45 (81.8)		1.00
35–54	244	178 (73.0)	0.008	0.89 (0.77–1.03)
≥55	33	17 (51.5)		0.63 (0.44–0.90)
Duration of NIDDM (yr)				
<4	159	104 (65.4)		1.00
4–7	121	94 (77.7)	0.034	1.19 (1.03–1.38)
8–11	25	22 (88.0)		1.35 (1.12–1.62)
≥12	27	20 (74.1)		1.13 (0.88–1.45)
FPG (mM)				
<7.8	126	64 (50.8)		1.00
7.8–11.0	94	79 (84.0)	<0.001	1.65 (1.36–2.00)
≥11.1	112	97 (86.6)		1.71 (1.42–2.06)
Blood pressure (mmHg)				
Systolic				
<130	155	97 (62.6)		1.00
130–159	154	124 (80.5)	0.001	1.29 (1.12–1.49)
≥160	23	19 (82.6)		1.32 (1.06–1.65)
Diastolic				
<85	189	125 (66.1)		1.00
85–94	94	77 (81.9)	0.014	1.24 (1.08–1.43)
≥95	49	38 (77.6)		1.17 (0.98–1.40)
Hypertension status				
No	225	157 (69.8)	0.138	1.00
Yes	107	83 (77.6)		1.11 (0.97–1.27)
Cholesterol (mM)				
<6.2	285	203 (71.2)	0.287	1.00
≥6.2	47	37 (78.7)		1.11 (0.94–1.31)
Triglycerides (mM)				
<28.3	251	177 (70.5)	0.204	1.00
≥28.3	81	63 (77.8)		1.10 (0.96–1.27)
BMI (kg/m^2)				
<28	77	55 (71.4)		1.00
28–33	129	93 (72.1)	0.968	1.01 (0.85–1.21)
≥34	126	92 (73.0)		1.02 (0.85–1.22)
Smoking				
No	199	147 (73.9)	0.407	1.00
Yes	132	92 (69.7)		0.94 (0.82–1.08)
Renal Disease†				
No	264	188 (71.2)	0.388	1.00
Yes	68	52 (76.5)		1.07 (0.92–1.25)
Macrovascular disease‡				
No	214	158 (73.8)	0.398	1.00
Yes	118	82 (69.5)		0.94 (0.81–1.09)
Therapeutic regimen				
Diet alone	120	66 (55.0)	<0.001	1.00
Oral agent	165	139 (84.2)		1.53 (1.28–1.82)
Insulin	43	32 (74.4)		1.35 (1.06–1.71)

*Calculated by methods described by Morris and Gardner (22).

†Creatinine > 133 μM (1.5 mg/dl) or proteinuria.

‡Includes angina, myocardial infarction, electrocardiogram abnormality, stroke, and claudication.

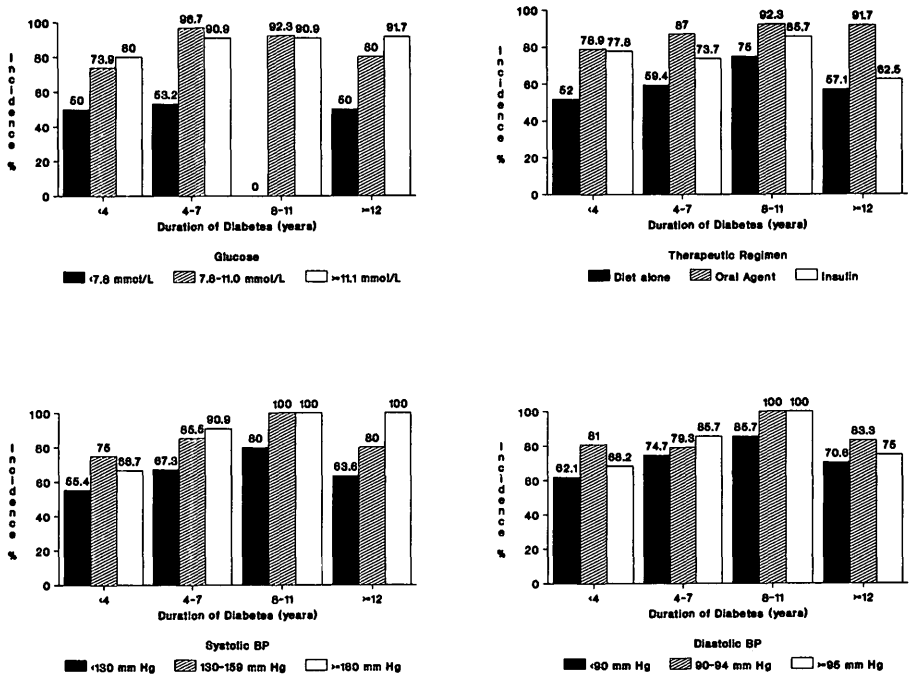

Figure 1—*Incidence of retinopathy by risk factors stratified by duration of diabetes at baseline examination. All variables were recorded at baseline examination.*

terview was between 8 and 12 yr. These risk factors also remained significant when stratified by age at diagnosis, with those diagnosed at younger ages at higher risk (data not shown).

Systolic and diastolic blood pressure and therapeutic regimen also remained significant when stratified by plasma glucose levels. For participants with plasma glucose levels <7.8 mM (140 mg/dl), hypertension was a significant risk factor in the development of retinopathy; however, for levels ≥7.8 mM (140 mg/dl), the incidence of retinopathy was high, ~≥83%, independent of hypertension (Fig. 2).

With respect to the relationship between initial therapeutic regimen and the development of retinopathy, the highest risk was associated with oral agents, followed by insulin, and lastly, diet restriction. We suspected that during the follow-up interval, therapeutic changes may have occurred. In a review of self-reported therapeutic regimens, we found that 56.3% of participants who were initially on oral agents reported that they had been using insulin an average of 8.2 yr by the time of follow-up; 29% originally on diet restriction reported daily insulin use at follow-up. The cumulative incidence of retinopathy when stratified by therapeutic regimen at follow-up were as follows: diet alone, 47.1%; oral agent, 66.4%; and insulin, 82.2%.

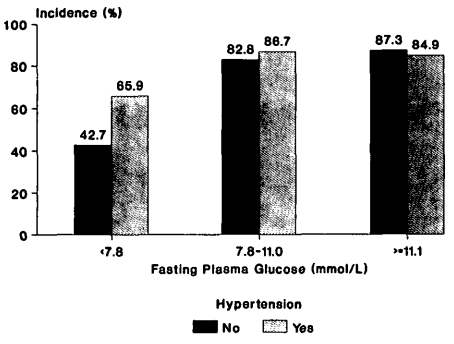

Figure 2—*Incidence of retinopathy by hypertension, stratified by FPG level. Both variables were measured at baseline. Hypertension is defined as systolic blood pressure ≥160 mmHg, diastolic pressure ≥95 mmHg, or use of antihypertensive medication.*

Risk factors for retinopathy incidence were also analyzed with multivariate models. A stepwise multiple logistic procedure was performed where the dependent variable was the presence or absence of retinopathy at follow-up, and the independent variables were sex, age, duration of diabetes, systolic and diastolic blood pressure, hypertension status, FPG, plasma triglyceride, plasma cholesterol, BMI, the presence of renal or macrovascular disease, and initial therapeutic regimen. Various models were fitted with and without interaction terms. When there was no interaction terms, we found that elevated FPG, use of therapeutic regimen (oral agent or insulin), higher systolic blood pressure, and longer duration of diabetes increased significantly the risk of developing retinopathy. On the other hand, patients who were older at baseline had a lower chance of developing retinopathy. The only significant interaction was found between FPG and hypertension. The maximum-likelihood value of the model including this interaction was significantly ($P < 0.05$) higher than that of the model without the interaction, indicating that the model with interaction provided a better fit of the data. Table 4 lists the four significant variables in order of their entry into the regression equation: FPG by hypertension, therapeutic regimen, age at baseline, and duration of diabetes. The results for glucose and hypertension were consistent with those presented in Fig. 2.

CONCLUSIONS— In our follow-up study of 927 Oklahoma Indians, of the 332 participants who did not have retinopathy at initial examination and who were available for a second eye examination, we found a cumulative incidence rate of 72.3% over a follow-up period of 10–16 yr. Our results are limited to

Table 4—*Risk factors related to cumulative incidence of retinopathy (logistic regression analysis)*

	Regression coefficient	RR 95% CI	*P*
FPG × HTN*			<0.001
FPG = 0 HTN = 1	0.883 ± 0.413	2.42 1.08–5.43	
FPG = 1 HTN = 0	2.216 ± 0.364	9.17 4.49–18.72	
FPG = 1 HTN = 1	1.721 ± 0.441	5.59 2.36–13.68	
Initial therapeutic regimen†			<0.001
Oral Agent	1.278 ± 0.318	3.59 1.92–6.69	
Insulin	0.320 ± 0.459	1.38 0.56–3.39	
Age	−0.052 ± 0.018	0.95 0.92–0.98	0.005
Duration of diabetes	0.071 ± 0.037	1.07 1.00–1.15	0.042

FPG = 1: FPG ≥7.8 mM. FPG = 0: FPG <7.8 mM. HTN = 1: SBP ≥160 mmHg or DBP ≥95 mmHg or on antihypertensive medication. HTN = 0: SBP <160 mmHg and DBP <95 mmHg and not on antihypertensive medication. *P* determined by likelihood ratio test.

*Relative to FPG = 0 and HTN = 0.

†Relative to dietary restriction alone.

crude incidence rates because no frequent eye examinations were conducted during the follow-up period to enable a more precise determination of the onset of diabetic retinopathy. Because of the long follow-up period, our results may be biased toward a population that has survived other diabetic complications. Those nonparticipants who were deceased at the time of follow-up were known to have had a higher prevalence of retinopathy at the initial examination compared with participants. Death certificates rarely mentioned retinopathy, and information from medical records was incomplete. Those nonparticipants who were alive had baseline characteristics comparable to the participants. It is unlikely that their incidence rates would have differed greatly from that of the participants. The high rate of mortality in our study may have resulted in an underestimate of incidence.

To the best of our knowledge, no other incidence rates for retinopathy among diabetic Oklahoma Indians are available. The prevalence data from West et al.'s (15) study of the same population showed a 24.4% prevalence among Oklahoma Indians with a mean age of 46 yr. Another study reported a prevalence of 49.3% among an older cohort of 142 diabetic Oklahoma Indians with a mean age of 55.8 yr (23).

Our incidence results are comparable with those reported for population-based studies. In a retrospective cohort study in the Radcliffe Diabetic Clinic, among patients who were diagnosed with diabetes between 30 and 59 yr of age, ~40% developed retinopathy 5–9 yr after initial examination (24). Among Swiss diabetic patients who were diagnosed with diabetes after age 30 yr and who were using insulin, ~35% developed retinopathy after 8 yr when diagnosed by direct ophthalmoscopy (25). In the Wisconsin Epidemiologic Study, among 191 insulin-taking patients with at least 5 yr of diabetes, 21% developed retinopathy >2 yr and 71% after 6 yr, as diagnosed by fundus photographs (26). The prevalence of retinopathy among diabetic Pima Indians has been estimated to be 18% (27). A crude incidence of retinopathy was reported to be >60% over a 6-yr period among Pima Indians treated with insulin (28), which may be comparable to our rate of ~74% over 12 yr among Oklahoma Indians using insulin at baseline.

The most significant risk factor for diabetic retinopathy in our study was fasting plasma glucose level. These results are consistent with previous reports and may lend support to research that suggests that the pathogenetic mechanisms responsible for the disease may involve elevated levels of sugar alcohols resulting in damage to the retinal vessel walls (29,30).

Blood pressure, especially systolic pressure, was a significant risk factor, which when stratified by glucose levels appeared most significant for patients with lower glucose levels. When blood glucose was ≥11.1 mM (200 mg/dl), no risk factors were significant except duration of diabetes. In our study, patients with diabetes between 8 and 12 yr were at highest risk for developing retinopathy. However, only a few participants who had diabetes ≥12 yr at baseline survived through the follow-up period. Our results may reflect a subpopulation of Oklahoma Indians who, after 12 yr of diabetes without retinopathy, may be less susceptible to developing it, and who may be less susceptible to other life-threatening diabetic complications as well. When adjusting for other risk factors by multivariate analysis, duration of diabetes remained a significant independent risk factor for retinopathy.

The presence of microvascular disease of the kidney has been significantly correlated with the prevalence of retinopathy among our population of diabetic Oklahoma Indians (15). However, we did not find renal disease to be a risk factor for the development of retinopathy. Our results are affected by the low survival rates of those participants who had renal disease at baseline. Nevertheless, we observed a significant correlation between renal disease and retinopathy among those participants who survived (data not shown).

With an estimated incidence of 72.3% for a cohort followed over an average 12 yr, diabetic retinopathy clearly poses a formidable health threat to the diabetic Oklahoma Indians. Early therapeutic intervention with photocoagula-

tion has been shown to reduce progression of the disease and subsequent visual impairment (31,32). Our examination of medical records revealed that, of 40 patients who had retinopathy at follow-up, only 20 had the disease diagnosed during the follow-up period and recorded in the chart. Health education on the importance of frequent ophthalmological examinations and timely photocoagulation therapy are clearly indicated in addition to efforts to prevent and control the development of diabetes in Oklahoma Indians. Given that hyperglycemia and hypertension are significant predictors of the development of diabetic retinopathy, the role of glycemic and hypertensive control in reducing the risk of retinopathy deserves further investigation.

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