Proliferative Retinopathy in NIDDM

Incidence and Risk Factors in Pima Indians

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The incidence of proliferative diabetic retinopathy was determined in the Pima Indians of the Gila River Indian Community in Arizona. Over 4 yr, this complication developed in 25 of 953 subjects ≥9 yr of age with non-insulin-dependent diabetes. No cases were diagnosed in <35-yr-old subjects, and the incidence was strongly related to the duration of diabetes. The cumulative incidence of proliferative retinopathy after 20 yr duration was 14%. All cases of proliferative retinopathy occurred in subjects with background retinopathy. Younger age at diagnosis of diabetes was associated with a higher incidence of proliferation when subjects with diabetes of similar duration were compared. A higher incidence of proliferative retinopathy, after controlling for age, sex, and diabetes duration, was associated with hypertension, proteinuria, renal insufficiency, absence of Achilles tendon reflex, elevated total serum cholesterol concentration, and insulin therapy. *Diabetes* 38:435–40, 1989

Proliferative retinopathy is a vision-threatening microvascular complication of diabetes in which new vessels grow on the surface of the retina and into the vitreous body. Subsequent hemorrhages and fibrous tissue proliferation, often associated with retinal detachment, cause severe impairment of vision. A previous study found that the incidence of proliferative retinopathy is greater in insulin-dependent (IDDM) than non-insulin-dependent (NIDDM) diabetes mellitus when people with similar duration of diabetes are compared (1). This suggests that different factors may be related to the development of proliferative retinopathy in each type of diabetes. Although proliferative retinopathy has been the focus of intensive clinical investigation, much remains unknown regarding the risk factors for this diabetic complication.

In this study, the incidence of proliferative retinopathy among people with diabetes was determined in the Pima Indians of the Gila River Indian Community in Arizona, a population in whom IDDM is unknown (2,3) but who have the world's highest reported incidence and prevalence of NIDDM (4). Predictors of proliferative retinopathy were identified, and the incidence of this complication in diabetic Pima Indians was compared with reports from other populations. Retinal lesions are very rare in nondiabetic Pimas, but typical diabetic retinopathy occurs in the diabetic subjects (5).

Glucose 1 mM = 18 mg/dl

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MATERIALS AND METHODS

The National Institutes of Health has conducted a longitudinal study of diabetes and its complications in the Gila River Indian Community of Arizona since 1965 (6). This community is inhabited primarily by Pima and Papago Indians. Approximately every 2 yr, each resident of the community who is at least 5 yr of age is asked, regardless of health, to participate in a standardized medical examination.

These biennial examinations include direct ophthalmoscopy performed by a physician (after pupillary dilation in subjects at least 15 yr of age). Background retinopathy was considered present if the subject had one or more microaneurysms, exudates, or hemorrhages. Proliferative retinopathy was considered present if the subject had neovascularization or vitreous hemorrhage, rubeosis iridis, or retinal detachment believed to be due to neovascularization of diabetic origin. Blood pressure was measured in the right arm with the subject at rest in the supine position. Systolic and diastolic blood pressures were measured at the first and fourth Korotkoff sounds, respectively.

Laboratory tests performed at each biennial examination included measurement of serum cholesterol and creatinine

concentrations, urine protein and creatinine concentrations, and a modified oral glucose tolerance test (OGTT) with determination of the glucose concentration in venous plasma drawn 2 h after the ingestion of a 75-g carbohydrate load (Glucola, Ames, Elkhart, IN; Dexcola, Custom, Baltimore, MD). Diabetes was diagnosed according to World Health Organization criteria (7), i.e., if the 2-h postload plasma glucose concentration was ≥11.1 mM (200 mg/dl). The date of diagnosis of diabetes was determined from biennial examinations, or from review of clinical records if diabetes was diagnosed in the course of routine medical care. Subjects were asked to void at the beginning of the OGTT, and a urine specimen was collected 2 h later. The presence of protein in the 2-h urine was determined by dipstick (Labstix, Ames). Urine specimens containing at least a trace of protein on dipstick were tested quantitatively for protein by the method of Shevky and Stafford (8). The concentration of creatinine was measured in the same urine specimen, and the protein-to-creatinine ratio was calculated. This ratio was used to approximate 24-h protein excretion, on the assumption that the daily excretion of creatinine averages ~10 mmol/day (1.13 g). Proteinuria was defined by a protein-to-creatinine ratio of ≥113 mg/mmol (1.0 mg protein/mg creatinine), equivalent to a total protein excretion rate of ~1g/day (9,10). Renal insufficiency was defined by a serum creatinine concentration of ≥177 μM (2.0 mg/dl).

The study population used in this analysis (953 subjects) consisted of all diabetic people (the youngest was 9 yr old) who lived in the Gila River Indian Community at any time between 13 October 1983 and 30 November 1987; whose heritage was at least 50% Pima, Papago, or a mixture of these closely related tribes; and who had undergone biennial research examinations.

A register of patients with proliferative diabetic retinopathy who received laser photocoagulation in the ophthalmology department of the Phoenix Indian Medical Center, the referral center for this population, was used to identify members of the population who had laser-treated proliferative retinopathy during the study. This log was established 13 October 1983, the starting date of our investigation. Before this date, patients were referred to other facilities for laser therapy, and no treatment records were available. The diagnosis of proliferative retinopathy was based on clinical examination by an ophthalmologist, supplemented when indicated by fluorescein angiography. To ensure detection of all recognized cases of proliferative diabetic retinopathy, the biennial examination records were also searched for subjects in whom proliferative retinopathy was noted at a biennial examination. The clinical record of each subject with proliferative retinopathy was reviewed to determine the date of first diagnosis of this complication (in either eye) by an ophthalmologist. In subjects who had proliferative retinopathy identified at biennial examination, the date of this examination was used as the date of diagnosis, if the diagnosis was subsequently confirmed by an ophthalmologist. Any subjects with proliferative retinopathy not diagnosed at a biennial examination or not seen by an ophthalmologist, or who, if seen, refused laser therapy, could not be identified.

Analytic methods. Incidence was expressed as the number of cases of proliferative diabetic retinopathy per 1000 person-yr of observation for diabetic subjects within the community. The numerator was the number of subjects who had proliferative retinopathy diagnosed between 13 October 1983 and 30 November 1987, and the denominator was all people with diabetes. The period of risk began on 13 October 1983 or the date of first biennial examination for subjects entering the study after this date; it extended to the date of diagnosis of proliferative retinopathy, death, emigration from the community, or close of the study (30 November 1987), whichever was earlier. The experience of subjects who entered the study on 13 October 1983 was accumulated according to the data available at that time based on their most recent biennial examination before this date. People who developed diabetes during the study period began to accumulate person-time from the date of diagnosis of diabetes.

Cumulative incidence was estimated from the incidence rates observed during the study period and represents the percentage of subjects who would have proliferative retinopathy at the end of each specified period of diabetes duration if the duration-specific incidence rates were constant during these intervals and all subjects survived until the end of each period (11).

The effects of variables representing potential risk factors for proliferative diabetic retinopathy were analyzed among subjects at least 35 yr of age (no cases of proliferative retinopathy occurred below this age) by Cox's proportional-hazards function (the BMDP P2L program; 12,13), which takes varying periods of follow-up and time-dependent changes of covariate values into account. Data for each subject were taken from the most recent biennial examination before the opening date of the study or, for subjects diagnosed with diabetes during the study, from the biennial examination at which the diagnosis of diabetes was made. In addition, values for variables under consideration were taken from all subsequent biennial examinations and, if these values changed, the new values were included for the appropriate periods. Subjects with data missing at initial examination were excluded from these analyses. Each variable was tested, controlling for the covariates age, sex, and duration of diabetes. Body mass index (BMI), calculated as weight (kg) divided by the square of height (m), was used as a measure of obesity. A quadratic function for diabetes duration was included because a nonlinear relationship between duration and the incidence of proliferative retinopathy was found. In addition, the natural logarithms of cholesterol concentration, 2-h postload plasma glucose concentration, and BMI were used in the analyses to normalize their distributions. The small number of cases did not permit a multivariate analysis controlling for all variables simultaneously.

RESULTS

During the study period, 953 diabetic subjects ≥9 yr of age (738 of whom were at least 35 yr of age) were at risk of developing proliferative retinopathy. Among them, 25 people (13 men, 12 women), all ≥35 yr, were recognized as having developed proliferative retinopathy. Twenty-three cases were diagnosed in the course of routine medical care, and 2 cases were initially identified at a biennial examination. All identified cases received laser therapy, and none was initially treated with vitrectomy.

Age- and sex-specific incidence rates of proliferative retinopathy are presented in Table 1. After controlling for age

TABLE 1
Incidence rates of proliferative retinopathy in diabetic Pima Indians

	Men			Women		
Age (yr)	Person-yr at risk	*n*	Incidence*	Person-yr at risk	*n*	Incidence*
5–34	203.0	0	0	361.1	0	0
35–44	344.3	6	17.4	360.8	0	0
45–54	304.6	4	13.1	504.9	5	9.9
55–64	238.5	3	12.6	409.3	5	12.2
≥65	177.6	0	0	353.8	2	5.7

*Cases/1000 person-yr at risk (1983–1987).

and diabetes duration, rates in men and women were not significantly different, with a male-to-female rate ratio of 1.5 (95% confidence interval, 0.7–3.4). The incidence rate of proliferative retinopathy was highest in those 35–44 yr of age among men and 55–64 yr of age among women. When the analysis was controlled for sex and duration of diabetes in a proportional-hazards model, younger subjects had a significantly greater incidence than older subjects of similar diabetes duration. A 10-yr age difference corresponded to an incidence-rate ratio of 0.6 (95% confidence interval, 0.4–0.9). The incidence of proliferation rose with increasing duration of diabetes, reaching a peak at 15–20 yr, and then declined (Fig. 1). Diabetes duration was a highly significant predictor of proliferative retinopathy (χ^2 = 24.1, df = 2, $P < .001$), when controlled for age and sex. The cumulative incidence of proliferative retinopathy as a function of the duration of diabetes is shown in Fig. 2. At 20 yr duration, the cumulative incidence was 14.1%.

The effects of several variables on the incidence of proliferative diabetic retinopathy in the diabetic population ≥35 yr of age are presented in Table 2. Seventeen people, none of whom developed proliferative retinopathy, were excluded from the proportional-hazards models because of missing data. In addition to age and duration of diabetes, the presence of hypertension, proteinuria, and renal insufficiency, absence of the Achilles tendon reflex, elevation of the total serum cholesterol concentration, and treatment with insulin were each significantly associated with the development of proliferative retinopathy, when controlled for age, sex, and diabetes duration. The 2-h postload plasma glucose concentration was positively associated and BMI negatively associated with proliferative retinopathy, but neither association was statistically significant when controlled for age, sex, and diabetes duration. Smoking was not predictive of proliferative retinopathy. The effects of proteinuria, hypertension, absence of the Achilles tendon reflex, and type of diabetes treatment as a function of diabetes duration are shown in Fig. 3.

Background retinopathy was the most important predictor of the risk of proliferative retinopathy, as it occurred in all cases before proliferation. To determine whether the strength and relative importance of risk factors for proliferative retinopathy in the 424 subjects with background retinopathy differed from those in the diabetic population as a whole, the same analyses were performed among the diabetic subjects who had background retinopathy. Person-time in these subjects was accumulated only after a biennial examination in which background retinopathy was diagnosed. This restriction resulted in the loss of four cases in whom background retinopathy was first diagnosed after the last biennial examination but before the recognition of proliferative reti-

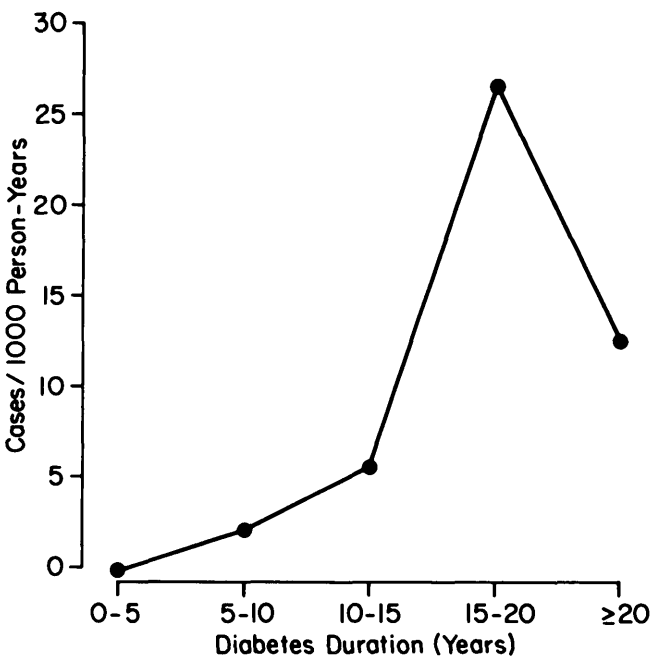

FIG. 1. Incidence (cases/1000 person-yr) of proliferative retinopathy in diabetic Pima Indians ≥35 yr of age as function of diabetes duration. Incidence is age and sex adjusted to 1980 Pima Indian population.

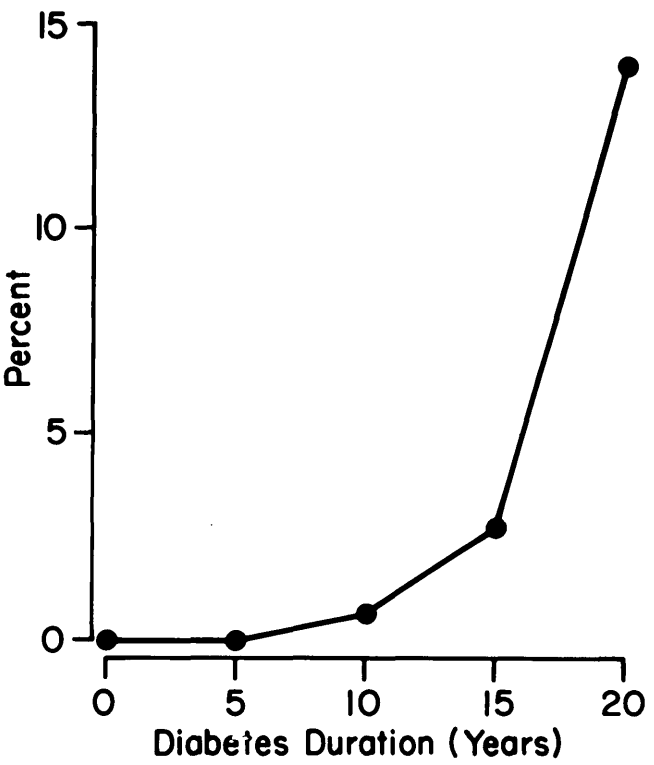

FIG. 2. Cumulative incidence (percentage) of proliferative retinopathy in diabetic Pima Indians as function of diabetes duration.

TABLE 2
Data for variables representing potential risk factors for proliferative retinopathy in diabetic Pima Indians ≥35 yr of age

Variable	Person-yr at risk	*n*	Incidence-rate ratio
Proteinuria*			
No	2277	14	
Yes	380	11	2.5 (1.1–5.8)
Renal insufficiency†			
No	2509	22	
Yes	43	3	4.8 (1.3–17.6)
Hypertension‡			
No	1832	11	
Yes	828	14	2.2 (1.0–4.9)
Smoking§			
No	1950	20	
Yes	594	5	0.7 (0.2–1.9)
Achilles tendon reflexes			
Present	1130	4	
Absent	1531	21	4.4 (1.3–14.9)
Treatment protocol‖			
No drug	1419	4	
Oral medicine	612	5	1.5 (0.4–6.3)
Insulin	631	16	3.5 (1.5–8.1)
2-h postload plasma glucose (mM)¶			
<16.0	875	5	
16.0–23.0	934	7	
≥23.1	845	13	1.3 (0.9–1.7)
Serum cholesterol (mM)¶			
<4.2	815	5	
4.2–4.7	938	5	
≥4.8	900	15	1.8 (1.2–2.7)
Body mass index (kg/m²)¶			
<28	857	12	
28–33.9	990	8	
≥34	843	5	1.0 (0.6–1.6)

Total number of person-years is not the same for each variable because of missing values. Incidence-rate ratios (with 95% confidence intervals) computed with Cox's proportional-hazards function analysis with time-dependent covariates controlled for age, sex, and diabetes duration (12,13). Ranges are in parentheses.
*Urine protein-to-creatinine ratio ≥113 mg/mmol (1.0 mg protein/mg creatinine), equivalent to a total protein excretion rate of ~1 g/day (9,10).
†Serum creatinine concentration ≥177 μM (≥2.0 mg/dl).
‡Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.
§History of smoking within 1 yr of biennial examination.
‖Incidence-rate ratios computed for oral medicine/no drug and insulin/no insulin.
¶Analyzed as continuous variables on a logarithmic scale. Rate ratios computed for a 25% increment in the values of these variables.

nopathy. Forty-six people (including the 4 cases) were excluded from the proportional-hazards model because of missing data. The findings of the risk-factor analyses were similar to those for the entire diabetic population (data not shown).

DISCUSSION

Many studies of proliferative retinopathy in NIDDM have been hindered by the inability to assess accurately the duration of diabetes. This is a serious limitation because the onset of NIDDM is insidious, and in the United States nearly half of the people with this type of diabetes remain undiagnosed (14). This could lead to an overestimation of the incidence rate of retinopathy in a population not routinely screened for diabetes. On the other hand, without systematic ophthalmologic screening, proliferative retinopathy may be missed, resulting in an underestimation of the incidence. In the present study, the duration of NIDDM is known with reasonable accuracy because Pima Indians are frequently tested for diabetes with OGTTs. Furthermore, all people participating in these tests undergo retinal examination.

Nevertheless, the incidence rates of proliferative retinopathy determined in this study may underestimate the actual rate because subjects with proliferative retinopathy not treated with photocoagulation, or not diagnosed at biennial examination or during routine clinical care, would have escaped detection. On the other hand, more complete ascertainment of cases may have occurred in subjects who were in worse health because such patients may have had more frequent and intensive examinations in the course of routine clinical care. However, despite the possibility of more complete ascertainment among the more ill patients, some of the cases may have been too ill to receive photocoagulation therapy. The inclusion in the denominator of any surviving cases of proliferative retinopathy occurring before 13 October 1983 contributed to a slight underestimation of the incidence rate during the study.

Mitchell (15) reported that the incidence of proliferative retinopathy among diabetic subjects with preexisting background retinopathy who attended a diabetic center in Newcastle, Australia, was 2%/yr. This compares with a rate of 0.9%/yr in our study in those ≥35 yr of age (25 cases in 2684 person-yr, Table 1). However, Mitchell's results included both IDDM and NIDDM subjects, among whom rates may differ.

Nielsen (16) determined the incidence of proliferative retinopathy in diabetic subjects from the island of Falster, Denmark, but only in those treated with oral hypoglycemic agents or with diet alone. During 1 yr of observation, 1% of the diabetic subjects and 2% of those with preexisting background retinopathy developed proliferative disease. Although the subjects followed by Nielsen had NIDDM, people treated with insulin were excluded. As illustrated by our study, this may cause a substantial underestimation of the overall incidence of proliferative retinopathy. Pima Indians treated with insulin have rates (controlling for age, sex, and diabetes duration) 3–4 times as high as those not receiving insulin. Supporting this observation is a report by Teuscher et al. (17) of a yearly incidence of proliferative retinopathy among subjects whose diabetes was diagnosed at ≥30 yr of age (primarily subjects with NIDDM) of 1.4% for those treated with insulin and 0.5% for those not treated with insulin.

Dwyer et al. (1) described a population-based investigation of proliferative retinopathy in 1135 diabetic patients in Rochester, Minnesota. The date of diagnosis of diabetes was determined from clinical records, and proliferative retinopathy was identified by ophthalmologists during the course of routine diabetes care. The cumulative incidence of proliferative retinopathy after 20 yr of diabetes duration was 3.8% in obese and 2.0% in nonobese subjects with NIDDM. By contrast, in those with IDDM, the 20-yr cumulative incidence was 20.0%. These differences might be due to more complete ascertainment of cases in subjects with IDDM or to differences in risk factors associated with each type of

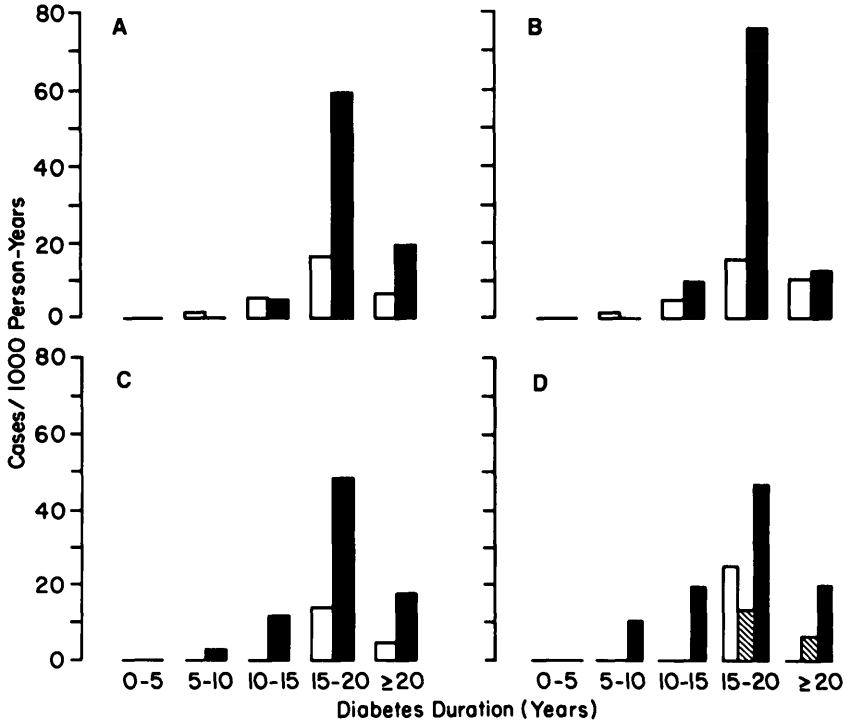

FIG. 3. Incidence (cases/1000 person-yr) of proliferative retinopathy in diabetic Pima Indians ≥35 years of age as function of diabetes duration, according to presence (*solid bars*) or absence (*open bars*) of hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) (*A*); proteinuria (*B*); or Achilles tendon reflex (*C*); and treatment with no drug (*open bars*), oral hypoglycemics (*hatched bars*), or insulin (*solid bars*) (*D*). Incidence is age adjusted to the 1980 Pima Indian population.

diabetes. The reasons for the discrepancy between that study and the much higher rate for NIDDM in our study (14% at 20 yr duration) are unknown. Racial and environmental differences, however, may be partly responsible.

In contrast, and although not directly comparable to our study, Klein et al. (18) reported the prevalence of proliferative retinopathy in patients whose diabetes had been diagnosed at ≥30 yr of age and had ≥15 yr duration of diabetes. The prevalence was 20.1% in those treated with insulin and 4.3% in those not treated with insulin, with an overall prevalence of 15.5%. This figure appears to be in much greater accord with the cumulative incidence in Pima Indians. The use of ophthalmoscopic photography, however, may have resulted in identification of a higher proportion of the affected cases.

A number of risk factors for proliferative retinopathy were identified in this study. The limited follow-up (maximum of 4 yr), however, and the relatively small number of incident cases may limit the power to identify other potentially important risk factors. In addition, any bias in the detection of cases toward a more or less healthy group could have an impact on the findings of this study. Greater detection of cases among members of the diabetic population with such factors as proteinuria, renal insufficiency, or hypertension would result in stronger apparent associations with such factors.

All cases of proliferative retinopathy occurred in subjects with preexisting background retinopathy, suggesting that proliferation seldom, if ever, develops de novo in the absence of background diabetic retinopathy. Previous longitudinal studies have also found that most proliferative retinopathy occurs in subjects already known to have background retinopathy (1,15,17). When the analysis of risk factors was restricted to subjects with background retinopathy, the factors predicting progression to proliferation were similar to those in the total diabetic population and showed similar incidence-rate ratios.

The duration of diabetes was an important determinant of proliferative retinopathy, with 84% of the cases occurring in subjects with diabetes duration of ≥15 yr. This is not surprising, because diabetes duration is a prominent risk factor for background retinopathy, which invariably preceded proliferation. However, after 20 yr of diabetes, there was a decline in the incidence of proliferative disease. This suggests that there may be a subset of diabetic individuals who are susceptible to proliferation, and that those who do not develop this complication within the first 20 yr of diabetes are less likely to be susceptible to it. This observation contrasts with that reported in IDDM of long duration where no decline in the incidence of proliferation has been found (19), but is analogous to the decline reported in incidence of nephropathy after 15 yr of IDDM (20,21).

The use of insulin predicted proliferative as well as background retinopathy in this population (22). The most likely explanation is that insulin users have more severe underlying diabetes. This is supported in that the 2-h postload plasma glucose concentration was positively (but not significantly) associated with the incidence of proliferative retinopathy. Whether improved glycemic control can reduce the incidence of proliferative retinopathy is not known. Glycemic control, however, may not be very effective in preventing the progression of retinopathy in IDDM (23,24).

In our study, hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) was significantly associated with the development of proliferative diabetic retinopathy and has been previously shown to predict the incidence of retinal exudates (22). The finding that blood pressure is predictive of background and proliferative retinopathy has potential therapeutic implications, but requires further investigation. The optimal mode of antihypertensive therapy for preventing diabetic complications and the level of blood pressure that should be treated are yet to be determined.

Although an association between proliferative retinopathy and smoking has been reported by some workers (25,26) and not by others (27), no association was found in the Pima Indians. However, among the Pima Indians <1% smoke a pack or more of cigarettes per day, and an association, if one were to exist, would be unlikely to be recognized.

An association between diabetic retinopathy and nephropathy has long been recognized. In our study, both proteinuria and renal insufficiency predicted proliferative retinopathy, even after controlling for age, sex, and duration of diabetes. The predictive effect of total serum cholesterol concentration is at least partially explained by its association with the renal impairment. Cholesterol may play a part, however, in the pathogenesis of diabetic retinopathy. Dornan et al. (28) reported that low-density lipoprotein cholesterol was significantly correlated with the severity of retinopathy after standardizing to creatinine clearance.

The risk factors identified as important predictors of proliferative retinopathy in our study are in general agreement with the conclusions from other populations (15,18,29,30). In addition to previously recognized risk factors, the absence of the Achilles tendon reflex was predictive in Pima Indians.

In conclusion, proliferative retinopathy is a frequent vision-threatening complication of NIDDM. Despite a number of potential biases, which could lead to underestimation of the incidence of proliferative retinopathy in our study, rates were comparable to or higher than those reported in other diabetic populations. The cumulative incidence of proliferative retinopathy in Pima Indians at 20 yr duration of diabetes was 14%. Background retinopathy occurred in all cases before the development of proliferative disease. Factors associated with the development of proliferative retinopathy include duration of diabetes, younger age, presence of hypertension, proteinuria, and renal insufficiency, absence of the Achilles tendon reflex, elevation of the total serum cholesterol concentration, and treatment with insulin.

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