Incidence of Diabetic Retinopathy and Relationship to Baseline Plasma Glucose and Blood Pressure

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A nationwide, stratified population sample of 534 diabetic Swiss men and women, aged 35–54 yr, participated in a study of vascular disease. The study was based on a common protocol, standardized examination procedures, and centralized laboratory methods. Patients were chosen from a pool of diabetic Swiss with diabetes ≥1 yr. After selection, the participants were classified into groups according to age at diabetes onset (>30 or <30 yr) and insulin treatment status. Several variables thought to be related to retinopathy incidence were analyzed at the initial examinations: onset of diabetes before age 30, duration of disease, fasting plasma glucose, blood pressure, and insulin therapy. Follow-up examinations of 358 of 458 survivors, with a diabetes duration that averaged 20 yr, showed retinopathy significantly and independently associated with initial fasting plasma glucose, systolic blood pressure, and insulin use but not with diabetes duration. Lower rates of retinopathy development were observed during the follow-up period in diabetic patients on antihypertensive therapy at the baseline examination, suggesting that not only lower fasting plasma glucose and systolic blood pressure levels but also blood pressure therapy itself decreases the incidence of retinopathy. *Diabetes Care* 11:246–51, 1988

For >30 yr the natural history and effects of interventions on the course of diabetic retinopathy have been under intensive study (1–7). Our investigation is partly an outgrowth of World Health Organization (WHO) recommendations to study, with cost-effective procedures, diabetic complications in a population setting. We felt that this study could help to fulfill the need for population research that would include clinical application to regions where technology is often limited.

This study relates the experience of 534 Swiss diabetic patients participating in an investigation coordinated at the Diabetes Center of the Medical Department at the University of Bern. Patients were first examined in 1974–1975 as part of a larger, multinational WHO study. Subsequently, a second survey was completed in 1982–1983. The results of the second examination allowed the calculation of incidence rates, as seen in this report.

MATERIALS AND METHODS

The study group comprised 278 diabetic men and 256 diabetic women 35–54 yr old under the care of 231 local practitioners from all parts of Switzerland in 1974. Participants were selected at random from a nationwide pool of all diabetic patients receiving care from family physicians and were stratified into groups according to age, gender, and diabetes duration but not microvascular or macrovascular complications. All were examined for the presence of vascular lesions according to a standardized protocol of the WHO study (1). Standardized clinical diagnostic procedures were used during data collection in the WHO study of 6695 diabetic men and women 35–54 yr old. The diabetes center had no foreknowledge regarding the prevalence of diabetic complications among the group and did not know whether the patients were on insulin, oral hypoglycemic agents, or diet therapy alone.

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Baseline examinations were performed in 1974–1975; morbidity and mortality follow-up was completed in 1982–1983, and calculations of prevalence and incidence rates were done for small- and large-vessel disease for a mean period of 8 yr. A more detailed description of the population, baseline protocol, and results of the prevalence study are described in detail in previous reports (1,2). Data collected by the patients' physicians included a standardized questionnaire (1) and venous fasting samples for plasma glucose (Hexokinase autoanalyzer). The questionnaire asked for the patient's age, duration of diabetes, height, weight, blood pressure (first measurement at rest in a sitting position), antihypertensive treatment, and diabetes therapy (1). Blood glucose was measured in the central laboratory of the University Hospital of Bern with quality control by the Centers for Disease Control (Atlanta, GA). Hypertension was considered present if the patient met at least one of the following criteria: systolic blood pressure ≥160 mmHg, diastolic pressure >95 mmHg, or use of antihypertensive medication.

Specially trained board-certified ophthalmologists at five university centers and other diabetes clinics examined the retinas by direct ophthalmoscopy through dilated pupils (≥5-mm diam) for 2 min, according to a standard protocol. Of the patients, >60% were seen by the 10 primary ophthalmic examiners at the departments of ophthalmology at the university medical schools in Bern, Basel, and Lausanne. At the follow-up examination, >75% of the patients were seen by the same ophthalmologist as at the baseline examination. Reference photos from the Hammersmith Hospital, London, were used to grade the lesions (2).

TABLE 1
Baseline characteristics for examination 2 respondents and nonrespondents

Baseline characteristic	Participants	Nonparticipants	
		Alive	Dead
n			
Men	184	38	39
Women	174	43	22
Age (yr)*			
Men	44.6 ± 6.5	45.3 ± 6.3	47.6 ± 6.1
Women	44.9 ± 6.3	44.2 ± 8.1	46.1 ± 6.2
Diabetes duration (yr)*			
Men	12.0 ± 8.4	8.5 ± 5.7	14.2 ± 10.9
Women	11.8 ± 8.0	10.1 ± 7.2	17.0 ± 8.7
Retinopathy at examination 1 (%)			
Men	32	16	43
Women	24	23	82
Nephropathy at examination 1 (%)			
Men	6.5	5.3	28.2
Women	18.3	4.8	58

*Data are means ± SD.

Of the original population of 534 diabetic patients, 39 men and 22 women died in the 8-yr period, and 15 others could not be located. Of the 458 survivors, 392 (86%) returned for reexamination. The eye examination was repeated in 358 (78%) patients, and these examinations represent the basis of this report. Comparisons of baseline characteristics for those reexamined and those who did not return can be made from Table 1. Examination 1 retinopathy prevalence (see criteria below) and nephropathy (presence of sulfosalicylic acid proteinuria) are also given according to examination 2 participation status (1). There was considerably more baseline small-vessel disease in those who died in the interval between examinations 1 and 2. No significant differences were found for age or diabetes duration.

On the basis of available data, and to conform to analyses undertaken by other investigators (8), individuals were classified according to age at onset of diabetes and treatment status. All diabetic participants with diabetes onset before age 30 yr were on insulin. Overall, 50% of men and 60% of women used insulin (1). Three groups were thus defined: *1*) early onset with insulin treatment (n = 160, 30% of total), i.e., onset of diabetes before age 30 yr requiring insulin continuously from the time of diagnosis (at least 1 yr); *2*) later onset with insulin treatment (n = 235, 44% of total), i.e., onset of diabetes at ≥30 yr of age requiring insulin; and *3*) later onset without insulin treatment (n = 139, 26% of total), i.e., onset of diabetes at ≥30 yr of age but not requiring insulin during the observation period.

Retinopathy data were collated, and four diabetic retinopathy variables were defined according to severity. The diagnostic criteria were agreed on by the investigators who participated in the WHO study (1). The four classes were as follows: *1*) Minimal or no retinopathy was diagnosed if there was no or only one small red lesion or one hard or soft exudate. Individuals with only one lesion were included in this class because their evidence of retinopathy was thought to be weak or doubtful. *2*) Nonproliferative retinopathy was diagnosed if there was more than one small, medium, or large red lesion or more than one soft or hard exudate. *3*) Proliferative retinopathy was diagnosed when there were well-defined new vessels. *4*) Retinopathic blindness was an endpoint classification assigned to patients who were recorded as blind or severely visually handicapped when this was due to or associated with new vessel formation, vitreous hemorrhages, or opacities.

Standard descriptive statistics were used in most of the analyses. Retinopathy progression to the more severe classes of retinopathy was calculated per 1000 person-yr, and the midpoint (4 yr) of the follow-up interval (8 yr) marked the occurrence of the event. Two-tailed Student's t tests were used to assess the likelihood that differences between group means were due to chance. Cross-classified groups were tested by 2 × 2 contingency tables. A stepwise multiple logistic regression procedure (SAS system, PROC LOGIST) was used to test

TABLE 2
Prevalence of retinopathy at examinations 1 and 2

Group	Age at diabetes onset	Insulin user*	*n*	Retinopathy (%) 1	Retinopathy (%) 2
1	<30 yr	Yes	105	51 (17.5)	70 (25.5)
2	>30 yr	Yes	159	25 (8.2)	60 (16.2)
3	>30 yr	No	94	9 (13.3)	20 (21.3)

Duration of diabetes (yr) is indicated in parentheses.
*At examination 1; implies therapy for ≥1 yr.

associations between independent variables and retina outcomes.

RESULTS

The prevalence of diabetic retinopathy in group 1 was 51% after a mean duration of diabetes of 17.5 yr and 70% at the second examination, when the mean duration was 25.5 yr. Group 2 had a diabetic retinopathy prevalence of 25% after a mean duration of 8.2 yr and 60% after 16.2 yr of diabetes. Similarly, group 3 had a retinopathy prevalence of 9% after 13.3 yr of diabetes and 20% after 21.3 yr (Table 2).

The distribution of retinopathy at examination 1, according to duration of diabetes, is presented in Fig. 1. Proliferative retinopathy is particularly associated with diabetes duration, and its occurrence is rare for diabetes of <10 yr duration. On the other hand, nonproliferative retinal disease is uncommon when diabetes duration is <10 yr, at its maximum between 15 and 30 yr duration, and less frequent with diabetes <30 yr duration.

The frequency of the four retinopathy classes at examination 2, according to baseline retinal findings, are shown in Table 3. Most individuals remained at the same retinopathy level as they were categorized at baseline. Among the insulin users, groups 1 and 2, there were no significant differences in the proportion progressing from no retinopathy at examination 1 to minimal disease at examination 2, whereas group 3 (without insulin) showed significantly lower rates of retinopathy development (χ^2 = 11.37, P = .0086, 1 df). The data are too sparse to make statements about progression for patients with nonproliferative disease or proliferative disease at baseline. There appears to be some regression of nonproliferative disease at baseline to less severe disease at examination 2, based on the direct ophthalmoscopy grading technique. Ten (12%) of 83 individuals were categorized this way.

The relationship between the incidence of new retinopathy (nonproliferative and proliferative) and fasting plasma glucose at the first examination are shown in Fig. 2. Higher quintiles of blood glucose are generally

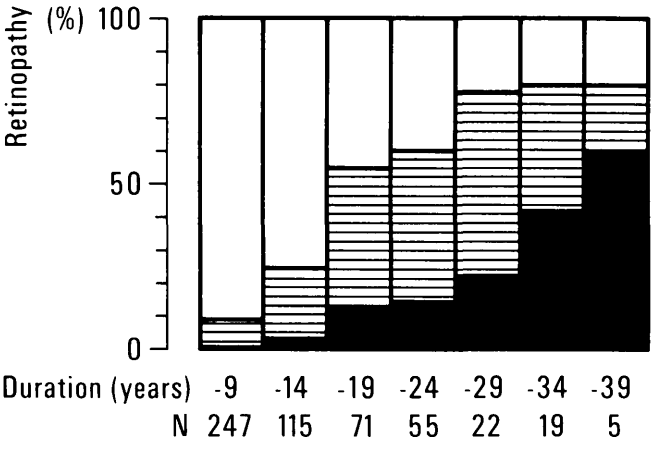

FIG. 1. Prevalence of diabetic retinopathy (*black area,* proliferative; *hatched area,* nonproliferative) at baseline examination according to diabetes duration at entry for 534 participants.

TABLE 3
Incidence of retinopathy and blindness in 358 Swiss diabetic patients in 8-yr period

Retinopathy at examination 1	Retinopathy at examination 2 (%) Minimal or none	Nonproliferative	Proliferative	Blindness	*n*
None or minimal					
Group 1	52	39	9	0	53
Group 2	52	40	8	0	120
Group 3	82	15	3	0	86
Nonproliferative					
Group 1	13	62	25	0	39
Group 2	3	69	22	6	36
Group 3	50	25	13	12	8
Proliferative					
Group 1	0	0	54	46	13
Group 2	0	0	33	67	3
Group 3					0

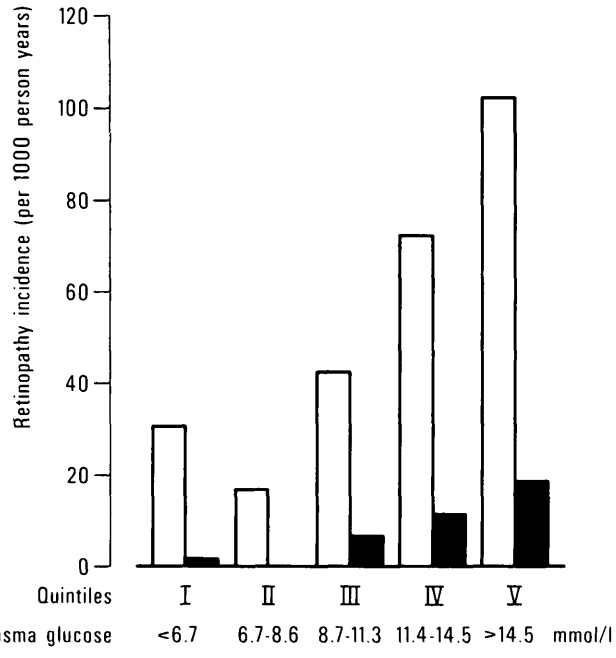

FIG. 2. Incidence of nonproliferative (*open bars*) and proliferative (*closed bars*) retinopathy per 1000 person-yr by quintile of venous fasting plasma glucose at baseline examination.

associated with more frequent retinopathy. Rates for nonproliferative disease are ~10 times greater than those for the more severe proliferative disease, and such a relationship is seen for most of the plasma glucose levels. Blood glucose quintile was highly correlated with the occurrence of new retinopathy ($P < .0001$, $n = 275$). Analysis by retinopathy severity showed initial fasting glucose was associated with development of nonproliferative retinopathy ($\chi^2 = 15.05$, $P = .001$, $n = 249$) and with proliferative retinopathy when the baseline retinal examination was either normal or showed nonproliferative disease ($\chi^2 = 15.63$, $P < .0001$, $n = 182$).

Nonproliferative and proliferative retinopathy incidences were analyzed with multivariate models that selected all diabetic patients with minimal or no retinopathy at the first examination. A stepwise multiple logistic procedure was performed. The dependent variable was the presence or absence of new retinopathy, and the independent variables were gender, age, duration of diabetes at examination 2, and the baseline factors systolic blood pressure and fasting plasma glucose. This model was computed for the total study population. The only variable significantly associated with retinopathy incidence in the model was the fasting glucose from examination 1 ($P < .0001$). The computations for each group revealed that there was no significant variable in group 1, only blood glucose was significant for group 2 ($P = .0002$), and blood glucose ($P = .0003$) and systolic blood pressure ($P = .027$) were significant in group 3.

Based on data from examination 1, subjects were classified into three systolic blood pressure groups (<141, 141–160, >160 mmHg) and subgrouped according to antihypertensive medication use. The incidence of nonproliferative retinopathy rose significantly with systolic pressure. Individuals with systolic pressures >140 mmHg exhibited the highest rates (Fig. 3). On the other hand, rates for developing proliferative retinopathy were much lower. Separate multivariate logistic analyses were performed according to blood pressure–treatment status, regressing new retinopathy on age, diabetes duration, and systolic blood pressure group. Systolic pressure was significantly associated with the adverse outcome among those not on antihypertensives ($P = .024$), but no significant association was seen between new retinopathy and blood pressure group for individuals taking antihypertensives ($P = .47$, NS).

DISCUSSION

There is a growing body of information from natural-history studies and clinical trials concerning the incidence of diabetic retinopathy (5,6,9–11). Results depend to a great extent on methodologies used, diabetes type, and definitions of diabetic retinopathy. This prospective study was designed to work with a standardized protocol that can be followed by practicing physicians with inexpensive techniques available in clinical practices throughout the world (12). Although modest in comparison with other studies, this study does provide incidence of new retinopathy and estimates of the progression of existing retinal disease in a random sample of diabetic patients with a longer duration of diabetes (mean of 20 yr at follow-up) than often studied (Fig. 1).

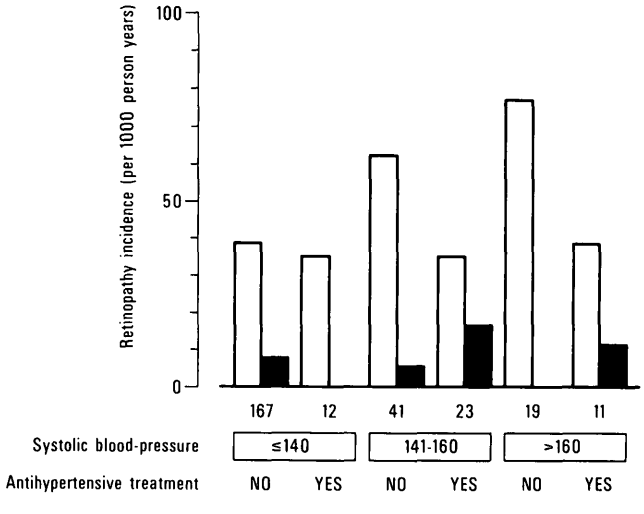

FIG. 3. Incidence of nonproliferative (*open bars*) and proliferative (*closed bars*) retinopathy in hypertensive and nonhypertensive, treated and untreated diabetes. Rates are shown per 1000 person-yr. Number of subjects in each group is indicated.

The incidence of new diabetic retinopathy (nonproliferative, proliferative, and blindness) per 1000 person-yr was almost identical in insulin-user groups of early and late onset (groups 1 and 2) and was much less frequent in the non-insulin-treated group (group 3) (Table 3). If nonproliferative retinopathy was present at examination 1, progression to proliferative retinopathy (~35%) was twice as frequent in the insulin-treated groups (groups 1 and 2) compared with those free of retinopathy and not taking insulin at baseline (16.7% of group 3). No diabetic patients with minimal or no retinopathy or members of the early-onset group with nonproliferative retinopathy at examination 1 progressed to blindness during follow-up. On the other hand, proliferative retinopathy at baseline was the most common precursor of blindness during follow-up, regardless of treatment-group status. Because the present study was not a trial, we cannot say that insulin had an adverse effect on the development of diabetic retinopathy. The more likely explanation is that insulin users had more severe underlying diabetes mellitus.

The baseline prevalence of retinopathy was similar for women reexamined (24%) and not reexamined (23%). However, in men not returning for examination 2, the baseline prevalence of retinopathy (16%) was half the rate of men who returned for examination 2 (32%) (Table 1). These data indicate that incidence is not obscured by dropout of diabetic patients, with more retinopathy at baseline. On the other hand, prevalence of retinopathy at baseline for those who died during the follow-up interval was high for both sexes (43% in men, 82% in women). This finding indicates a high mortality risk among individuals, particularly women, with diabetic retinopathy at baseline.

The results from this Swiss population are in accord with the estimated 35–50% prevalence of retinopathy for several cross-sectional surveys in patients with diabetes for 5–10 yr but are lower than the estimated 95% prevalence at 15 yr duration in early-onset insulin-dependent diabetes (8,13). Prevalence and incidence of retinopathy were compared with the results of the population-based study by the Kleins and their co-workers in Wisconsin (5,6). The prevalence of diabetic retinopathy for diabetes of 5–10 yr duration was much higher in the Wisconsin study (60%) than in the Swiss study. However, the Wisconsin study had broader definitions of retinopathy (one microaneurysm, hard or soft exudate) and more sensitive methods (panretinal photography).

It has been suggested for many decades that plasma glucose is an important risk factor in diabetic retinopathy, but this theory has not been universally proved in large-scale studies (9,14–19). Our investigation only had available a single fasting venous plasma glucose determination at baseline and affords only a crude index of habitual glycemic status, particularly in the insulin-treated individuals. Despite its inadequacies, our study revealed a highly significant relationship between the single fasting plasma glucose values at examination 1 and retinopathy incidence for individuals >30 yr old.

Glucose seems to be a risk factor for new retinopathy in individuals with onset after age 30, regardless of insulin treatment status. In the early-onset diabetic group treated with insulin, plasma glucose could not be identified as a significant risk factor. The factor most likely to be responsible for this lack of effect is the large biologic variation of fasting plasma glucose in the younger diabetic patients before they took their morning insulin. The advent of tests such as the HbA_{1c} assay, which represents average glucose levels over the preceding weeks, may help to improve classification of such individuals. Recent investigations have shown positive associations between such glycosylated hemoglobin levels and the occurrence of retinopathy (10,17). Unfortunately, such measurements were not available at the start of this investigation.

As in other studies, systolic blood pressure could also be identified as a significant risk factor in the incidence of retinopathy (16). With increasing systolic pressure the incidence of nonproliferative diabetic retinopathy is significantly greater in all three groups. Diabetic patients under antihypertensive treatment did not develop retinopathy in proportion to increased systolic pressure. Thus, treatment of early hypertension may have a protective effect on the development of diabetic retinopathy. For proliferative retinopathy no relationship to elevated systolic blood pressure was seen, but there were too few cases to ensure that no relationship exists.

On first inspection it may appear anomalous that diabetes duration was not associated with retinopathy incidence in this study. This study group included individuals with long-term diabetes: the average duration was 12 yr at entry and 20 yr at follow-up. Other descriptive studies, including those of long-term diabetes, showed similar results (15,20), and the rise in nonproliferative retinopathy ceased at 17-yr diabetes. Although duration of diabetes is an important factor in retinopathy, other factors such as blood pressure level, blood pressure therapy, and glycemic control may play increasingly important roles in diabetes of extremely long duration. The results of this study suggest that blood pressure and antihypertensive therapy at baseline are associated with a lower rate of retinopathy. Furthermore, retinopathy rates were positively associated with fasting plasma glucose levels at the time of the baseline examination. Clearly, more information on the importance of glycemic control is needed.

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