Risk Factors for Development of Retinopathy in Elderly Japanese Patients With Diabetes Mellitus

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OBJECTIVE — To define the risk factors for the development of diabetic retinopathy in elderly patients with diabetes mellitus.

RESEARCH DESIGN AND METHODS — We studied 110 diabetic outpatients >60 yr of age who were free of diabetic retinopathy at the first visit and were followed for at least 5 yr to examine the relationships between the initial findings and the subsequent development of retinopathy.

RESULTS — A total of 49 of the subjects developed diabetic retinopathy during the follow-up period; of these, 4 patients progressed to preproliferative and 3 to proliferative retinopathy. Univariate analysis showed that the initial fasting plasma glucose levels, the HbA_1 values, the 2-h postload plasma glucose levels, the estimated duration of diabetes, and the presence of persistent proteinuria were all associated with the development of diabetic retinopathy. However, age at the initial examination, estimated age at diabetes onset, sex, body mass index, type of therapy, and hypertension had little impact on the development of retinopathy. Stepwise multiple Cox regression analysis revealed that the initial HbA_1 or fasting plasma glucose, the diabetes duration, and the presence of persistent proteinuria are significant independent predictors for the development of retinopathy.

CONCLUSIONS — Initial fasting plasma glucose, diabetes duration, and proteinuria are important risk factors for the development of retinopathy in elderly patients with diabetes mellitus.

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FPG, FASTING PLASMA GLUCOSE; BMI, BODY MASS INDEX; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; BP, BLOOD PRESSURE; sBP, SYSTOLIC BLOOD PRESSURE; dBP, DIASTOLIC BLOOD PRESSURE; OGTT, ORAL GLUCOSE TOLERANCE TEST; CI, CONFIDENCE INTERVAL; RR, RELATIVE RISK.

Although glycemic control and diabetes duration are established risk factors for diabetic retinopathy in younger NIDDM patients (1–3), relatively few studies have examined the risk factors for retinopathy among older NIDDM patients. Two cross-sectional studies have shown that diabetes duration (4), HbA_{1c} levels (4), and age (5) are independent predictors of the presence of retinopathy in older diabetic patients. However, data on risk factors to predict the later development of retinopathy are not yet available. We have explored the risk factors for the development of diabetic retinopathy in 110 elderly diabetic patients who were free of retinopathy at the initial visit and who were followed for at least 5 yr.

RESEARCH DESIGN AND METHODS

— The medical records of 255 diabetic outpatients followed for at least 5 yr through January 1990 in the Endocrinology Section of the Tokyo Metropolitan Geriatric Hospital were examined, and 161 patients referred to the clinic between 1973 and 1985 with initial ages >60 yr were identified. At the time of the first examination, 48 (30%) of 161 patients had diabetic retinopathy, and 7 (4%) of these had proliferative retinopathy. Of those who were free of retinopathy at the first examination, 4 patients were excluded because of loss of data during follow-up. Therefore, 110 elderly diabetic patients free of retinopathy at the initial examination took part in the study.

Fundoscopic examinations of the retina (through dilated pupils) were performed at the initial visit by experienced ophthalmologists using direct ophthalmoscopy. Until the final ophthalmic examinations in 1990, all but 1 patient had annual (86%) or biennial (13%) ophthalmic examinations. Based on the ophthalmoscopic findings, the status of retinopathy was classified according to Fukuda's classification (6) and assigned to one of five categories: no retinopathy, mild background retinopathy (microaneurysms or

dot hemorrhages only in at least one eye), moderately severe background retinopathy (microaneurysms and blot hemorrhages, hard exudates, or macular edema), preproliferative retinopathy (cotton-wool spots, intraretinal microvascular abnormalities, or venous beading), and proliferative retinopathy (neovascularization of the disc and elsewhere, or vitreous hemorrhage believed to be attributable to diabetic neovascularization).

The development of retinopathy was defined as the new appearance of any retinopathy during the follow-up period. In 98% of the patients, the assessment of retinopathy development was confirmed in the final ophthalmic examinations; only 3 patients with microaneurysms regressed to no retinopathy.

At the first visit, we took a past medical history including previous treatment for diabetes and hypertension, past smoking, alcohol habits, and family history of diabetes. A standardized physical examination included the measurement of body height, weight, BP, and the presence of deep tendon reflexes. Hypertension was considered present if the patient met at least one of the following criteria: sBP ≥160 mmHg, dBP ≥95 mmHg, or use of antihypertensive drugs. Persistent proteinuria was defined as proteinuria ≥30 mg/dl in three or more successive urinalyses without evidence of urinary tract infection.

Blood was drawn for the determination of FPG, HbA_1, serum total cholesterol, and serum triglyceride levels. Sixteen patients first visited our clinic before 1980 when the measurement of HbA_1 was begun; therefore, their first HbA_1 values obtained in 1980 were considered baseline HbA_1. Ninety-five patients underwent an OGTT. After overnight fasting, a 50- or 75-g oral carbohydrate load was administered and 2-h postload plasma glucose levels were obtained. The values obtained from patients receiving the 50-g load were normalized to the 75-g values as described previously (7).

The cumulative incidence curves between the two groups were compared with the log-rank test. Univariate and multivariate (in a stepwise manner) Cox regression analyses were used to test the association between independent variables and the occurrence of retinopathy during the follow-up period.

Table 1—*Clinical characteristics of elderly diabetic patients at baseline*

Age (yr)	69.2 ± 5.5
Sex (M/F)	36/74
BMI (kg/m^2)	24.0 ± 3.8
Diabetes duration (yr)	6.9 ± 7.9
Treatment (diet/oral drugs/insulin)	64/43/3
FPG (mM)	10.0 ± 4.2
2-h postload plasma glucose (mM)	19.2 ± 6.4
HbA_1(%)	9.6 ± 2.5
sBP (mmHg)	148 ± 25
dBP (mmHg)	80 ± 14
Cholesterol (mM)	5.5 ± 1.1
Triglycerides (mM)	18.7 ± 9.4
Follow-up period (yr)	7.9 ± 2.6

Data are means ± SD.

RESULTS — The clinical characteristics of elderly diabetic patients free of retinopathy at baseline are shown in Table 1. Of the 110 elderly diabetic patients, 49 developed retinopathy during 719 person-yr of observation; the incidence rate was 68.2/1000 person-yr. Of these, 42 (86%) had background retinopathy; 4 patients progressed to preproliferative and 3 to proliferative retinopathy; and 7 (6%) patients developed macular edema.

The incidence of subsequent retinopathy in each clinical group according to the initial features is shown in Table 2. The development of retinopathy was more common in patients with higher FPG ($P < 0.001$), HbA_1 ($P < 0.05$), and 2-h postload plasma glucose (≥16.8 mM) levels ($P < 0.05$), a longer diabetes duration ($P < 0.05$), or persistent proteinuria ($P < 0.05$) at baseline (log-rank test).

In univariate analysis using Cox proportional hazards model, similar factors are significantly associated with the development of retinopathy (Table 2). However, age per se, age at diabetes onset, sex, BMI, type of treatment, family history of diabetes, BP, hypertension, serum cholesterol, serum triglycerides, smoking, and the consumption of alcohol were not significantly associated with retinopathy.

Stepwise multiple Cox regression analysis showed that the initial FPG ($P < 0.05$) (or alternatively the HbA_1 level [$P < 0.01$]), the diabetes duration ($P < 0.05$), and the presence of persistent proteinuria ($P < 0.01$) remained significant predictors for the development of retinopathy in elderly NIDDM patients.

CONCLUSIONS — This retrospective longitudinal study showed that hyperglycemia as measured by FPG and HbA_1 levels, long diabetes duration, and the presence of persistent proteinuria at the time of initial examination are independent risk factors for the development of retinopathy in elderly NIDDM patients. These results are consistent with follow-up data obtained in younger NIDDM patients (1–3,8).

In our study, ophthalmoscopic findings by ophthalmologists were used as the predominant method of screening. Although there was fair agreement in the detection of retinopathy between the ophthalmoscopic findings of the retinal specialist and the reading of ophthalmographs (9), we cannot completely exclude the possibility that a few microaneurysms were missed. However, this limitation probably does not detract from the overall conclusions. The closeness of the follow-up may have improved the sensitivity of ophthalmoscopic examinations. Alternatively, low sensitivity would tend to obscure the relationship between plasma glucose and the development of retinopathy. Thus, the association between plasma glucose and retinopathy may be stronger than is evident from our study.

In our study, neither the age at diabetes onset nor age at the time of the first visit was a predictor for the later development of retinopathy in the elderly NIDDM population. The finding that the age at diabetes onset had no

Table 2—*Univariate Cox regression analysis of the associations between clinical variables at baseline and the development of retinopathy in elderly Japanese diabetic patients*

	Incidence*	RR(95% CI)†	*P* value
Age (yr)			
60–69	59.4	1.21 (0.90–1.62)	0.20
≥70	77.7		
Age at onset (yr)			
<60	74.9	0.79 (0.59–1.05)	0.11
≥60	65.6		
Sex‡			
Men	60.2	1.17 (0.63–1.19)	0.62
Women	71.8		
BMI (kg/m^2)			
<25.0	75.5	0.89 (0.66–1.19)	0.43
≥25.0	57.9		
Diabetes duration (yr)			
<5	50.5	1.47 (1.13–1.91)	<0.01
≥5	91.4		
FPG (mM)			
<7.8	26.8	1.55 (1.19–2.02)	<0.01
≥7.8	91.8		
2-h postload plasma glucose (mM)			
<16.8	33.7	1.37 (1.04–1.80)	<0.01
≥16.8	82.8		
HbA_1 (%)			
<8.0	40.2	1.54 (1.20–1.98)	<0.001
≥8.0	82.8		
Hypertension‡			
Present	74.0	1.23 (0.69–2.18)	0.48
Absent	61.5		
Proteinuria‡			
Present	167.6	3.12 (1.31–7.40)	0.01
Absent	62.6		
Loss of Achilles tendon reflexes‡			
Present	94.6	1.69 (0.96–2.98)	0.07
Absent	56.4		

*Cases/1000 person-yr at risk.
†The estimates of RR are given as standardized estimates of the RR associated with one SD change of the continuous variable or as estimates of the RR of one category compared with the other.
‡Categorical variable.

effect is in agreement with a prospective study in diabetic patients not taking insulin (8), but is at variance with a population-based study in Rochester, which demonstrated that an earlier age of onset was a significant risk factor for the development of retinopathy and that the incidence of retinopathy decreased after 60 yr of age (3). As we included only diabetic patients >60 yr of age, some sampling biases exist in the selection of samples. Therefore, to clarify the relationship between age and the development of retinopathy, further studies are needed.

Regardless of the limitations of this study, our results suggest that a careful assessment of the risk factors for the development of retinopathy and careful management of diabetes during follow-up are as important in elderly patients with diabetes mellitus as they are in younger patients.

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