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Incidence of and risk factors for diabetic retinopathy in Isfahan, Iran

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Abstract

BACKGROUND Evidence on the incidence of and risk factors for diabetic retinopathy is mainly derived from studies in developed countries. Locally derived evidence is required for planning a well-coordinated approach to this public health problem in developing countries.

OBJECTIVE The objectives of the present study were to estimate the incidence of and risk factors for the development of diabetic retinopathy using routinely collected data from a clinical information system at the Isfahan Endocrinology and Metabolism Research Center, Iran, for non-insulin-dependent (insulin-treated and non-insulin-treated) diabetes.

METHOD During the mean (standard deviation (SD)) follow-up period of 5.1 (2.1) (range 1–9) years, 549 diabetic patients (161 male and 388 female) from the Isfahan Endocrinology and Metabolism Research Center outpatient clinics at Amin University Hospital, Iran, were examined. The mean (SD) age of the participants was 45.7 (9.3) years with a mean (SD) duration of diabetes of 6.9 (5.7) years at initial registration.

RESULTS Among the 549 patients free of retinopathy at initial registration with at least one follow-up visit between 1992 and 2001, the incidence of any retinopathy was 89.4 (95% confidence interval (CI): 79.0, 101.0) [96.1 (95% CI: 76.7, 118.0) in males and 86.6 (95% CI: 74.5, 99.9) in females] per 1000 person-years based on 2786 person-years of follow-up. The incidence rate of retinopathy was 60% greater among insulin-treated than non-insulin-treated non-insulin-dependent

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diabetes mellitus (NIDDM) clinic attenders. The incidence of any retinopathy was greater with older age, longer duration of diabetes, higher diastolic blood pressure and poor metabolic control. Using a Cox's Proportional Hazards Model for insulin-treated and non-insulin-treated NIDDM diabetes separately, poor metabolic control was a significant independent predictor of retinopathy for insulin-treated and non-insulin-treated NIDDM patients. When all variables were entered in the model, age, poor metabolic control and fasting blood glucose were significant predictors of retinopathy. In the insulin-treated group, fasting blood glucose was also a significant predictor of retinopathy. Systolic and diastolic blood pressure, gender, smoking, proteinuria, body mass index and creatinine had no significant independent association with retinopathy when other covariates were considered.

CONCLUSION These data suggest that diabetic retinopathy in this population of Iranian non-insulin-dependent diabetic patients is common, being found in almost half of the patients after a mean 5-year follow-up. Poor metabolic control is the major risk factor.

Key words Retinopathy incidence; diabetes mellitus; risk factors; Iran

Introduction Diabetic retinopathy is a common complication in people with diabetes. Diabetic eye disease and its complications, especially diabetic retinopathy, is a leading cause of blindness and visual dysfunction in adults in economically developed societies.[1,2] Epidemiological studies of the impact of diabetic eye disease in developing countries are scarce. Accurate information regarding the incidence of diabetic retinopathy and associated risk factors is important in the prevention of its development and of the visual impairment caused by this complication in these countries.

There is a growing body of information from observational studies and clinical trials regarding the incidence of and risk factors for diabetic retinopathy.[3–14] While there have been numerous studies in developed countries, few have been undertaken in developing countries, where the problem is greater. Diabetic retinopathy is a serious problem in Iran but to our knowledge, there have been no prospective studies describing its incidence or risk factors. We have examined this using routinely collected data from a clinical information system for diabetes at the Isfahan Endocrinology and Metabolism Research Center in Iran.

Patients and methods

DATA COLLECTION Clinical data are collected for all consecutive patients at the first attendance and at review consultations (usually annually) using standard encounter forms. These include an examination of ocular fundus, lens, limbs, blood pressure and construction of a problem list by the clinician, measurement of fasting blood glucose, glycosylated hemoglobin (HbA1), urinary protein, triglyceride, cholesterol and serum creatinine, and reporting of smoking as part of a completed questionnaire on demography, family history, and smoking by

the patient. A registry clerk enters data from these forms into the hospital computer after the clinic.

All of the patients were referred to an ophthalmology clinic. The diagnosis of retinopathy was first based on indirect ophthalmoscopy through dilated pupils. Then the diagnosis of retinopathy was confirmed (or not) by fundus photography. Any retinopathy was recorded as nonproliferative, maculopathy, or proliferative types. Nonproliferative retinopathy included microaneurysms, intraretinal hemorrhage, and hard exudates that the original examiner believed to be of diabetic origin. Maculopathy was defined as nonproliferative retinopathy causing a marked loss of visual acuity due to macular edema and was recorded only if specifically diagnosed. Proliferative retinopathy was defined by the presence of neovascularization or vitreous hemorrhage believed to be due to neovascularization of diabetic origin. The term 'any retinopathy' refers to both nonproliferative and proliferative retinopathy. Overall, the more severely affected eye defined the retinopathy level.

Many patients have retinopathy at diagnosis or develop it shortly afterwards. Since many patients were referred some years after diagnosis we have no means of knowing the relationship between the onset of diabetes and the development of retinopathy among those with this complication at the time of referral. Also, the onset of NIDDM may precede diagnosis by some years. This study was therefore confined to those who were clinically free of retinopathy at initial registration, recording the rate of development of retinopathy over subsequent years.

PATIENTS Between 1992 and 2001, a total of 9246 patients (3926 male and 5320 female) were registered in the system. Of these, 2040 (22.1%) patients were insulin-dependent or other types of diabetes and 7206 (77.9%) NIDDM. However, this study uses data only for 549 (161 male and 388 female) NIDDM patients who were free of retinopathy at registration and had at least one subsequent review and for whom complete data and fundus photography were available. Baseline characteristics of those selected and not selected are shown in Table 1. With the exception of a slightly shorter duration of diabetes, lower systolic blood pressure and fasting blood glucose, a higher proportion of females and insulin-treated diabetes and a lower proportion of current smokers, there were no significance differences in the characteristics of those who were selected compared to those who were not. The sample had similar distributions in age, age at diagnosis, diastolic blood pressure, HbA1, triglyceride, cholesterol, urea, creatinine, history of blood pressure and proteinuria, as those not selected. The 549 patients had a mean (standard deviation (SD)) duration of diabetes of 5.9 (5.7) years and a mean age of 44.6 (9.3) years. The average duration of follow-up was 5.4 (2.1) years (range 1–9 years).

Risk factors for the development of retinopathy were assessed using the following data from the patient's registration consultation: gender, age at diagnosis, age, duration of diabetes (the time between diagnosis and the baseline examination), body mass index (BMI) (weight/height^2 [kg/m^2]), smoking status (never, current), hemoglobin

Characteristics	*Participants*		*Non-participants*		*Différences (95% CI)*
	No.	*Mean (SD)*	*No.*	*Mean (SD)*	
Age at registration (yr.)	549	51.5 (9.5)	6649	52.4 (10.9)	−0.9 (−1.8, 0.04)
Duration of diabetes (yr.)	549	5.8 (5.5)	6636	6.7 (6.3)	−0.9 (−1.4, −0.3)*
Age at diagnosis (yr.)	549	45.7 (9.3)	6630	45.7 (10.7)	0.0 (−0.9, 0.9)
BMI (kg/m^2)	534	27.4 (4.5)	6470	27.3 (4.5)	0.1 (−0.3, 0.5)
Systolic BP (mmHg)	521	126.2 (21.1)	5856	128.3 (22.4)	−2.1 (−4.1, −0.1)**
Diastolic BP (mmHg)	508	78.3 (11.5)	5664	78.9 (12.1)	0.6 (−1.7, 0.5)
Fasting blood glucose (mg/dl)	549	200.1 (68.1)	6469	208.3 (75.2)	−8.2 (−14.4, −1.7)**
HbA1 (%)	467	10.6 (2.3)	3227	10.6 (2.4)	0.0 (−0.2, 0.2)
Triglyceride (mg/dl)	544	229.8 (163.7)	6208	234.6 (160.0)	−4.8 (−18.8, 9.3)
Cholesterol (mg/dl)	545	224.2 (49.7)	6231	226.4 (51.6)	−2.2 (−678, 2.3)
Urea (mg/dl)	534	28.3 (15.2)	5588	28.3 (12.9)	0.0 (−1.2, 1.2)
Creatinine (μM/l)	464	1.1 (1.4)	4070	1.0 (0.9)	0.1 (−0.01, 0.2)
		No. (%)		*No. (%)*	
Gender	549		6651		
Male		161 (29.3)		2850 (42.9)	−13.5 (−17.5, −9.5)**
Female		388 (70.7)		3801 (57.1)	–
Smoking					
Never-smoked	514	455 (88.5)	6075	5044 (83.0)	5.5 (2.6, 3.4)**
Current-smoker		59 (11.5)		1031 (17.0)	–
Blood pressure history	546		6558		
Present		246 (45.1)		3121 (47.6)	−2.5 (−6.9, 1.8)
Absent		300 (54.9)		3437 (52.4)	–
Proteinuria	395		3067		
Present		139 (35.2)		1007 (32.8)	2.4 (−2.6, 7.4)
Absent		256 (64.8)		2060 (67.2)	–
Therapeutic regimen	549		6657		
Insulin		113 (20.6)		1123 (16.9)	3.7 (0.2, 7.2)**
Non-insulin drug		436 (79.4)		5534 (83.1)	–

Note: Total of each variable may vary because of missing value. CI = Confidence interval.
*p < 0.05, **p < 0.001 for the difference in the mean and proportion of the variables between participants and non-participants.

TABLE 1. Group means and proportions comparison of selected baseline characteristics between participating and non-participating NIDDM patients.

A1 (HbA1) (measured by spectrophotometer) (as an indicator of diabetic control), fasting blood glucose, proteinuria, serum creatinine, triglyceride, cholesterol and blood pressure (BP) (systolic and diastolic) at registration. Diabetes treatment (insulin, oral agent, and diet alone) used in the analysis was that recorded at the last clinic visit. The physician defined the type of diabetes using the problem list.

ANALYSIS Statistical methods used included Student's t-test, chi square test, and stepwise Cox's Proportional Hazards Model, which takes varying periods of follow-up and time-dependent changes of covariate values into account, to test associations between baseline variables and retinopathy outcomes.[15–18] Two types of statistical analyses are presented in this report: Crude relative risk based on incidence

rates and adjusted relative risk determined by a forward stepwise Cox's Proportional Hazard Model using the SPSS for Windows computer package which simultaneously adjusts for other covariates. Risk factors examined included the participant's age, gender, age at diagnosis, duration of diabetes, fasting blood glucose, HbA1, BMI, proteinuria, creatinine, therapeutic regimen, systolic and diastolic BP, and smoking habits, all recorded at initial registration except therapeutic regimen which was recorded at the last clinic visit. For this analysis, follow-up time, age, age at diagnosis, duration of diabetes, fasting blood glucose, HbA1, systolic and diastolic blood pressure, BMI and creatinine were included as continuous variables. Gender, proteinuria and cigarette smoking (never and current) were entered as dichotomous variables. Therapeutic regimen (diet, oral agent and insulin) was included as a trichotomous variable. Likelihood ratio tests were selected for testing the significance of the coefficients. The likelihood ratio test made at each step determined if the last variable that entered the regression added significantly to the variables already selected. The forward stepwise procedures with 0.05 entry and removal criteria resulted in a ranking of the variables according to their relative importance. Incidence was expressed as the number of cases of retinopathy per 1000 person years of observation (in order to fully utilize the period of observation for each individual and properly weight their contribution to the study). The numerator was the number of patients who had retinopathy diagnosed between 1992 and 2001, and the denominator was person-times. The period of risk began on the date of first registration for patients entering the study after this date; it extended to the date of diagnosis of retinopathy, or date of last contact with registry, or close of the study. Patients who registered during the study period began to accumulate person-time from the date of registration. 95% CI for mean and proportion differences were estimated by confidence interval analysis software.[19]

Results

PATIENT CHARACTERISTICS AT REGISTRATION Differences in distribution of several risk factors among insulin-treated and non-insulin-treated NIDDM measured at initial registration are shown in Table 2. There were 436 (79.4%) non-insulin-treated NIDDM and 113 (20.6%) insulin-treated NIDDM patients. Patients with non-insulin treatment were older at the time of the initial registration, had shorter duration of diabetes, lower fasting blood glucose levels, lower HbA1 and higher cholesterol levels.

INCIDENCE OF RETINOPATHY Of the 549 patients, 249 (45.4%; 78 men and 171 women) developed retinopathy in a total of 2786 (812 male and 1974 female) person-years of follow-up. The other 300 diabetic patients had not developed retinopathy by the end of this study period. Overall incidence of any subsequent retinopathy was 89.4 per 1000 person-years (95% CI: 79.0, 101.0). Incidence rates were lower in women (86.6 per 1000 person-years (95% CI: 74.5, 99.9)) than in men (96.1 (95% CI: 76.7, 118.0)). This difference was not statistically signifi-

TABLE 2. Group means and proportions comparison of selected baseline characteristics between 113 insulin-treated and 436 non-insulin-treated NIDDM patients.

Characteristics	*Insulin-treated NIDDM*	*Non-insulin-treated NIDDM*	*Differences (95% CI)*
	Mean (SD)	*Mean (SD)*	
Duration of diabetes (yr.)	6.6 (6.3)	5.1 (5.1)	1.5 (0.4, 2.6)*
Age at diagnosis (yr.)	45.7 (10.4)	43.4 (11.8)	2.3 (−0.07, 4.7)
BMI (kg/m^2)	26.9 (5.4)	27.6 (4.3)	−0.7 (−1.7, 0.3)
Systolic BP (mmHg)	126.9 (23.4)	126.0 (20.5)	0.9 (−3.6, 5.4)
Diastolic BP (mmHg)	78.0 (11.6)	78.4 (11.5)	−0.4 (−2.9, 2.1)
Fasting blood glucose (mg/dl)	231.9 (72.2)	191.8 (64.6)	40.1 (26.4, 53.8)*
HbA1 (%)	11.3 (2.2)	10.4 (2.3)	0.9 (0.4, 1.4)*
Triglyceride (mg/dl)	208.5 (142.9)	235.4 (168.4)	−26.9 (−60.8, 7.0)
Cholesterol (mg/dl)	214.5 (42.5)	226.6 (51.2)	−12.1 (−22.4, —1.8)*
Urea (mg/dl)	29.4 (12.6)	28.0 (15.8)	1.4 (−1.8, 4.6)
Creatinine (μM/l)	1.3 (2.0)	1.1 (1.2)	0.2 (−0.1, 0.5)
	No. (%)	*No. (%)*	
Gender			
Male	34 (30.1)	127 (29.1)	1.0 (−8.5, 10.4)
Female	79 (69.9)	309 (70.9)	–
Smoking			
Never-smoked	90 (84.9)	365 (89.5)	−4.6 (−12.0, 2.9)
Current-smoker	16 (15.1)	43 (10.5)	–
Blood pressure history			
Present	44 (38.9)	202 (46.7)	−7.7 (−17.9, 2.4)
Absent	69 (61.1)	231 (53.3)	–
Proteinuria			
Present	35 (39.8)	104 (33.9)	5.9 (−5.6, 17.4)
Absent	53 (60.2)	203 (66.1)	–

*$p < 0.001$ for the difference in the mean and proportion of the variables between insulin treatment and non-insulin treatment; CI = Confidence interval

cant ($p > 0.05$). Of the 131 patients who had insulin-treated NIDDM but were free of retinopathy at initial registration, 72 subsequently developed retinopathy of one form or another, giving an incidence of 108.4 per 1000 person-years (95% CI: 84.8, 132.0). This was higher than the incidence rate seen for non-insulin-treated NIDDM: 83.4 per 1000 person-years (95% CI: 72.0, 96.0) ($p < 0.001$).

RISK FACTORS Table 3 shows the group means (SD) and proportions for those participants who did and did not develop any form of retinopathy. Those who developed retinopathy had higher systolic blood pressure (128.4 vs. 124.3 mmHg; $p < 0.05$), higher HbA1 levels (11.2% vs. 10.1%; $p < 0.001$), higher fasting blood glucose levels (206.7 vs. 194.6; $p < 0.05$), longer duration of diabetes (13.3 vs. 9.3 years; $p < 0.001$), and were older at registration (53.1 vs. 50.3; $p < 0.001$). A lower

TABLE 3. Group means and proportions for selected variables between 249 participants who did and 300 who did not develop any form of retinopathy.

Variables	*Retinopathy*	*No retinopathy*	*Difference 95% CI@*
	Mean (SD)	*Mean (SD)*	
Age at registration (yr.)	53.1 (9.4)	50.3 (9.4)	2.8 (1.2, 4.3)***
Duration of diabetes (yr.)	13.3 (6.7)	9.3 (5.0)	4.0 (3.0, 5.0)***
Age at diagnosis (yr.)	45.5 (9.1)	45.9 (9.5)	−0.4 (−2.0, 1.1)
BMI (kg/m²)	27.3 (4.6)	27.6 (4.5)	−0.3 (−1.1, 0.5)
Systolic BP (mmHg)	128.4 (20.8)	124.3 (21.2)	4.1 (0.5, 7.7)*
Diastolic BP (mmHg)	79.3 (11.2)	77.4 (11.6)	1.9 (−0.01, 3.9)
Fasting blood glucose (mg/dl)	206.7 (65.2)	194.6 (70.1)	12.1 (0.7, 23.5)*
HbA1 (%)	11.2 (2.4)	10.1 (2.2)	1.1 (0.7, 1.5)***
Creatinine (μM/l)	1.1 (1.1)	1.2 (1.6)	−0.1 (−0.4, 0.2)
Triglyceride (mg/dl)	224.0 (151.0)	234.6 (173.5)	−10.6 (−38.3, 17.1)
Cholesterol (mg/dl)	220.8 (49.7)	226.9 (49.7)	−6.1 (−14.5, 2.3)
Urea (mg/dl)	29.1 (14.2)	27.6 (16.0)	1.5 (−1.1, 4.1)
Uric acid (mg/dl)	4.9 (1.5)	4.7 (1.4)	0.2 (−0.2, 0.6)
	No. (%)	*No. (%)*	
Gender			
Male	78 (31.3)	83 (27.7)	3.7 (−4.0, 11.3)
Female	171 (68.7)	217 (72.3)	–
Smoking			
Never-smoked	32 (13.7)	27 (9.6)	4.0 (−1.6, 9.6)
Current-smoker	202 (86.3)	253 (90.4)	–
Proteinuria			
Present	82 (42.1)	57 (28.5)	13.6 (4.2, 22.9)**
Absent	113 (57.9)	143 (71.5)	–
Therapeutic regimen			
Diet	6 (2.4)	18 (6.0)	−3.6 (−6.9, −0.3)***
Oral agent	171 (68.7)	241 (80.3)	−11.7 (−19.0, −4.4)***
Insulin	72 (28.9)	41 (13.7)	15.2 (8.4, 22.1)***

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. The difference in the mean or percentage of the variables between retinopathy and no retinopathy. @CI = Confidence interval.

proportion of those who developed retinopathy had used diet (2.4% vs. 6.0%; $p < 0.001$) or oral agents (68.7% vs. 80.3%; $p < 0.001$), but a higher proportion had used insulin (28.9% vs. 13.7%; $p < 0.001$) and had proteinuria (42.1 vs. 28.5; $p < 0.01$).

A univariate analysis (Table 4) showed that age at registration, duration of diabetes, HbA1, diastolic blood pressure, proteinuria and therapeutic regimen were significantly associated with the risk of developing retinopathy. For all variables there was a fairly consistent 'dose response' across the range of values; for example, the risk of retinopathy was higher in older age groups, among patients with a longer duration of diabetes, proteinuria and higher diastolic blood pressure. The

TABLE 4. Incidence rates of retinopathy by baseline variables.

Variables	*At risk (No.)*	*Cases (No.)*	*Person-years*	*Incidence per 1000 person-years*	*Crude relative risk (95% CI)*	*Age-adjusted relative risk (95% CI)*[†]
Gender						
Female	388	171	1974	86.6	1.0	1.0
Male	161	78	812	96.1	1.1 (0.9, 1.3)	1.01 (0.9, 1.03)
Age at registration (yr.)						
<40	73	20	375	53.3	1.0	1.0
40–49	191	83	962	86.3	1.6 (1.1, 2.4)*	1.6 (1.1, 2.4)*
50–59	183	91	942	96.6	1.8 (1.2, 2.7)**	1.8 (1.2, 2.7)**
60–69	93	50	470	106.4	2.0 (1.2, 3.3)*	2.0 (1.2, 3.3)*
≥70	9	5	37	135.1	2.5 (1.01, 6.4)*	2.5 (1.01, 6.4)*
Age at diagnosis (yr.)						
<30	28	16	144	111.1	1.0	1.0
30–59	491	223	2502	89.1	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)
≥60	30	10	140	71.4	0.6 (0.3, 1.1)	0.6 (0.3, 1.1)
Duration of diabetes (yr.)						
<5	326	113	1602	70.5	1.0	1.00
5–7	73	39	361	108.0	1.5 (1.2, 2.0)**	1.1 (0.9, 1.5)
8–11	74	44	395	111.4	1.7 (1.4, 2.2)***	1.06 (0.8, 1.4)
≥12	76	53	428	123.8	2.0 (1.6, 2.5)***	1.1 (0.9, 1.4)
Fasting blood glucose (mg/dl)						
≤120	38	15	182	82.4	1.0	1.0
121–140	64	20	311	64.3	0.8 (0.5, 1.4)	0.8 (0.5, 1.1)
141–200	213	94	1094	85.9	1.1 (0.7, 1.7)	1.0 (0.8, 1.3)
>200	234	120	1196	100.3	1.3 (0.9, 2.0)	1.3 (1.0, 1.6)
HbA1 (%)						
≤9	129	40	611	65.5	1.0	1.0
9.1–11	219	105	1208	86.9	1.6 (1.2, 2.1)**	0.7 (0.5, 1.0)
11.1–13	92	50	539	92.8	1.8 (1.3, 2.4)***	0.7 (0.5, 1.0)
13.1–15	25	17	123	138.2	2.2 (1.5, 3.2)***	1.5 (0.9, 2.4)
>15	2	2	11	181.8	3.2 (2.5, 4.2)*	2.1 (0.7, 6.6)
Systolic BP (mmHg)						
<140	375	160	1951	82.0	1.0	1.0
140–159	85	47	416	113.0	1.4 (1.01, 1.9)*	1.3 (1.0, 1.6)
≥160	61	30	300	100.0	1.2 (0.8, 1.8)	1.0 (0.8, 1.3)
Diastolic BP (mmHg)						
<70	64	21	349	60.2	1.0	1.0
70–90	330	158	1702	92.8	1.5 (1.0, 2.4)*	1.1 (0.9, 1.3)
≥90	114	56	557	100.5	1.7 (1.03, 2.7)*	1.3 (1.03, 1.7)*
BMI (kg/m^2)						
<27	271	134	1428	93.8	1.0	1.0
27–33	225	92	1099	83.7	0.8 (0.7, 1.0)	1.1 (0.9, 1.4)
≥34	38	15	190	78.9	0.9 (0.6, 1.4)	0.9 (0.6, 1.3)
Smoking						
Never-smoked	455	202	2318	87.1	1.0	1.0
Current-smoker	59	32	318	100.6	1.2 (0.9, 1.6)	1.05 (0.9, 1.3)
Proteinuria						
Absent	256	113	1419	79.6	1.0	1.0
Present	139	82	803	102.1	1.3 (1.0, 1.7)	1.1 (1.0, 1.3)
Creatinine (μM/l)						
≤1.5	439	204	2321	87.9	1.0	1.0
>1.5	25	12	148	81.1	1.0 (0.7, 1.6)	0.8 (0.6, 1.1)
Therapeutic regimen						
Diet alone or Oral agent	436	177	2122	83.4	1.0	1.0
Insulin	113	72	664	108.4	1.6 (1.3, 1.9)***	1.0 (0.9, 1.2)

Total number of person-years and at risk is not the same for each variable because of missing values.
[†]Relative risks (with 95% CI) calculated by Cox's Proportional Hazard Model.[17]
*p < 0.5, **p < 0.01, ***p < 0.001.

insulin-treated NIDDM patients were more likely to develop retinopathy than non-insulin-treated NIDDM patients in this univariate analysis. Age-adjusted Cox regression coefficients among those free of retinopathy at registration showed that age and diastolic blood pressure were significant risk factors for developing retinopathy.

The incidence of retinopathy was also analyzed with a multivariate model. A stepwise Cox's Proportional Hazard Model was performed; 235 subjects were excluded from these analyses because of missing risk factors information, leaving 314 people to analyze for any incident retinopathy. Three separate models were computed for insulin-treated and non-insulin-treated NIDDM patients and all NIDDM together. Table 5 shows the association of these variables in order of their entry into the regression equation in each group. Poor metabolic control significantly increased the risk of developing retinopathy in all models. For the insulin-treated group, fasting blood glucose also increased the risk of developing retinopathy significantly. As expected, there was a statistically significant interaction between age and duration of diabetes. In the model, which included all types of diabetes, older ages at diagnosis and fasting blood glucose also significantly increased the risk of developing retinopathy. No other variables were significant.

Discussion In this follow-up study of 549 diabetes clinic attenders, we found an overall incidence of retinopathy of 89.4 per 1000 person-years (249 patients) over an average follow-up of 5.4 years. To the best of our knowledge, no other incidence rates for retinopathy among Iranian people have been reported. Incidence rates in various studies from around the world show considerable variation. One study from Taiwan among NIDDM found an incidence of diabetic retinopathy of 53.3 per 1000 person-years.[20] Another study from Denmark found 82.3

Variables	*Relative Risk*	*95% Confidence interval*
	Total	
Age (yr.)	1.03	1.006, 1.04**
Fasting blood glucose (mg/dl)	1.003	1.0003, 1.005*
HbA1 (%)	1.08	1.007, 1.15*
	Non-insulin-treated NIDDM	
HbA1 (%)	1.1	1.01, 1.2*
	Insulin–treated NIDDM	
Fasting blood glucose (mg/dl)	1.01	1.004, 1.01**
HbA1 (%)	1.2	1.05, 1.40**
Age*Duration of diabetes (yr.)	1.001	1.0005, 1.002*

*p < 0.05, **p < 0.01.

TABLE 5. Risk factors related to incidence of retinopathy for patients with insulin-treated and non-insulin-treated non-insulin-dependent (NIDDM) diabetes and both together (Cox's Proportional Hazard Model).

per 1000 person-years among the subjects treated with oral hypoglycemic agents.[21] In Minnesota, the incidence of diabetic retinopathy among NIDDM subjects was 15.6 per 1000 person-years.[3] In Wisconsin, after 4 years of follow-up, the observed incidence of diabetic retinopathy among subjects older than 30 years was 119.0[22] and after 10 years of follow-up 110.6 per 1000 person-years.[23] Another report from the San Luis Valley Diabetes Study, Colorado, among Hispanic and non-Hispanic whites with type-2 diabetes observed an incidence rate of 63.7 per 1000 person-years.[24] A very similar study to this, from Nottingham in the UK, showed an incidence of diabetic retinopathy in a clinic population of 59.6 per 1000 person-years.[25] The rates thus range from 15.6/1000 person-years in Rochester, Minnesota, using routine care follow-up, to 119.0/1000 person-years in the population of the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). Our clinic-based figure is higher than the values reported in Denmark, Taiwan, UK and the San Luis Valley Diabetes Study, but lower than the WESDR. The higher rates in our study could have been due to differences in medical care access and therapy, considering that Pugh et al.[26] have shown a higher prevalence of retinopathy among people without health insurance or with less comprehensive ambulatory care coverage. Lower rates in our study than in the WESDR could have been due to less complete follow-up of people with more severe diabetes or other factors. Because our patients were less likely to return for follow-up visits, our rates are probably underestimates of the true rates in this population. However, it seems that the incidence of diabetic retinopathy among diabetic patients in Isfahan was high.

Univariate analysis (Table 2) shows an expected pattern of association for many variables with the development of retinopathy. In multivariate analysis fewer variables remain independently associated. In this study, males had a slightly higher risk of developing retinopathy in univariate analysis. After adjusting for other confounders, gender was not a significant independent predictor, like in other studies.[26–28]

As other studies have shown, duration of diabetes was strongly associated with the incidence of retinopathy.[4,25,29–31] As in other studies, patients with diabetes for more than 8 years were at highest risk for developing retinopathy. When adjusting for other risk factors by multivariate analysis, duration of diabetes was not a significant independent risk factor for retinopathy. But there was a statistically significant interaction between age and duration of diabetes in the insulin-treated group and the effects of both variables were not independent.

In univariate analysis, we found that the incidence of any retinopathy was higher in insulin-treated NIDDM patients than in non-insulin-treated NIDDM patients. Insulin treatment may indicate a more severe disease process. Furthermore, the longer duration of diabetes, younger age at onset and poorer metabolic control than in non-insulin-treated NIDDM might be confounding factors. After adjustment for other covariates in the multivariate analysis, the type of treatment was not significant. The fact that the estimated relative risk for insulin-treatment was not statistically significant after adjustment for the other covariates indicates that a higher incidence of retinopathy among insulin-treated NIDDM patients could be attributed to their

longer duration of diabetes, younger age at onset and poorer metabolic control than in non-insulin-treated NIDDM.

The level of hyperglycemia, as measured by one glycosylated hemoglobin assessment at baseline, was found to be a strong and independent predictor of the incidence of diabetic retinopathy, which is comparable with previous studies.[4,30,32–38]

The effect of blood pressure on the risk of retinopathy is an important but difficult issue because blood pressure rises as duration of diabetes and age increase. Previous studies have yielded conflicting results. Some studies find no relationship;[13,25,39] however, in more recent studies, rates of retinopathy were related to blood pressure.[4,14,29,31,40] In univariate analysis, we found that the incidence of retinopathy was 70% higher in patients with diastolic BP over 90 mmHg compared with those whose diastolic BP was less than 70 mmHg. This association did not remain in multivariate analysis.

Previous studies differ in relation to the importance of obesity as a risk factor. By multivariate analysis, however, we found no association between BMI and retinopathy.

Although data from a few studies suggest a positive relationship between cigarette smoking and diabetic retinopathy,[41,42] most epidemiological studies have failed to confirm this relationship.[12,13,43–48] In this study, smoking (classified in two simple categories of never and current) was not related to incidence of retinopathy after correcting for other covariates. This lack of association may reflect some pattern of survivorship. Those who smoked at registration and continued to do so may have died of a smoking-related illness, including cardiovascular disease, neoplasia and other causes of death, before having the opportunity to develop retinopathy.

The Isfahan clinical information system for diabetes provides one of the largest clinic-based data sets of its kind in the developing world. Although we have not carried out any special studies of the validity or reliability of data for this analysis, previous studies show that these patients are a representative sample of the known diabetic patients in Isfahan.[38,49] Our experience with other parts of the data set gives us some confidence that data quality is sufficient for this type of study and that our results provide useful additional evidence on the incidence of and risk factors for retinopathy. The study was clinic-, rather than population-based, and so may not contain a clinical spectrum representative of diabetic patients in the community. Many patients requiring only oral or dietary treatment may never attend the clinic.[50] Clinic-based estimates of the incidence or prevalence of complications are most likely to be affected by referral patterns. Selection bias is less likely to affect incidence rates and associations between risk factors and complications[51] as investigated in this study.

Our diagnosis of retinopathy is not based on a single examination but on continuing examination during follow-up, using a problem list as the basis for further clinical decisions. All those with retinopathy will have been referred to an ophthalmology clinic and so had their diagnosis of retinopathy confirmed or not by an ophthalmologist through fundus photography. Nevertheless, several observers have made observations over the years, and problems of observer error need to be considered.

It seems reasonable to assume that observer error is independent of such variables as age, duration of diabetes, blood pressure and type of treatment of the patient. If this is so, misclassification resulting from observer error will tend to reduce rather than increase the significance of differences between groups of patients. Therefore, if a significant difference is found between two otherwise comparable groups of patients, it is reasonable to infer that it is not due to observer error but must reflect a true difference. Slight differences in baseline duration of diabetes, systolic blood pressure, fasting blood glucose, gender and smoking status between study participants and the entire population of registered diabetic patients could limit slightly the generalizability of our findings.

With an estimated incidence of 89.4 per 1000 person-years of observation, diabetic retinopathy clearly poses a formidable health threat to Iranian diabetic patients. Early treatment with photocoagulation has been shown to reduce progression of the disease and subsequent visual impairment.[52,53] The results of this study highlight the need for regular eye examination in people with diabetes.

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