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Four years incidence of diabetic retinopathy and effective factors on its progression in type II diabetes

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PURPOSE. *To study the 4 years incidence of diabetic retinopathy in patients with type II diabetes and effective factors on its progression.*

METHODS. *Among diabetic patients referred to Yazd Diabetes Research Center, 120 patients with type II diabetes without diabetic retinopathy were selected. After complete ophthalmic examination, fasting blood sugar (FBS), postprandial blood sugar, triglyceride, and cholesterol were measured and height, weight, and blood pressure (BP) were recorded. Then patients were followed with eye examination yearly for 4 years.*

RESULTS. *Four-year cumulative incidence of diabetic retinopathy was 47.5% (95% CI: 38.6–56.4). The retinopathy was mild nonproliferative diabetic retinopathy (NPDR) in 43 (35.8%) whereas 10 (8.3%) patients had moderate NPDR, 3 (2.5%) patients had severe NPDR, and only one patient had proliferative diabetic retinopathy. The incidence of diabetic retinopathy was 5.8% in first year, 20.3% in the second year, 24.4% in the third year, and 7.4% in the fourth year. Duration of diabetes, FBS, and systolic BP had statistically significant relation with grades of diabetic retinopathy. However, there was no significant association between age, sex, body mass index, triglyceride, cholesterol, method of treatment, smoking, and diastolic BP with grades of diabetic retinopathy.*

CONCLUSIONS. *These data provide 4-year cumulative incidence of diabetic retinopathy in defined type 2 diabetic patients. The present study shows that duration of diabetes, hyperglycemia, and systolic BP appear to be the major factors associated with the development of any level of retinopathy in type 2 diabetic patients. (Eur J Ophthalmol 2008; 18: 572-7)*

KEY WORDS. *Type II diabetes, Incidence, Diabetic retinopathy*

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INTRODUCTION

The chronic complications of diabetes mellitus (DM) affect many organs and are responsible for the majority of morbidity and mortality associated with this disease (1). Diabetic retinopathy (DR) is the most severe of the several ocular complications of diabetes. Advances in treatment over the past 40 years have greatly reduced the risk of blindness, but because diabetes is so common, retinopathy remains the most frequent cause of blindness among adults aged 20–74 years (WHO Study Group. Diabetes Mellitus. Technical Reports Series No. 727. Geneva World Health Organization, 1985). The importance of this problem is that the probability of blindness in diabetic patients is 25 times greater than in the nondiabetic population (2).

DR is classified in two stages: nonproliferative DR (NPDR) and proliferative DR (PDR). Proliferative retinopathy may occur in up to 50% of patients with type 1 diabetes (3) and in about 10% of patients with type 2 diabetes (4) who have had the disease for 15 years. Not all individuals with NPDR develop PDR, but the more severe the nonproliferative disease, the greater the chance of evolution to proliferative retinopathy within 5 years (5).

There are two opposing trends: we have better control of

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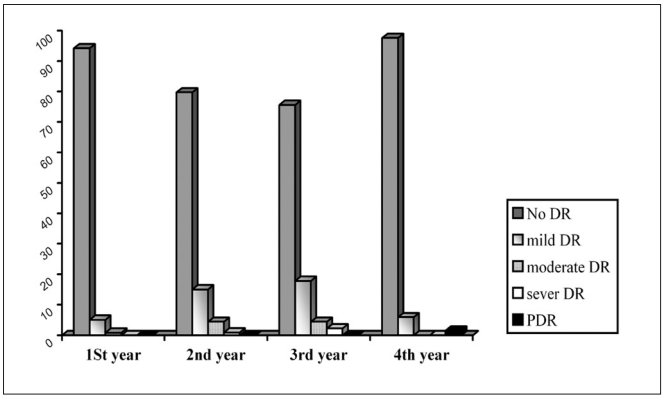

Fig. 1 - *Annually retinopathy incodence in 4 years following up of diabetic patients.*

diabetes and better treatment of DR, but the number of diabetic patients is increasing rapidly, so we expect to see more complications of diabetes. Therefore we need to reevaluate our epidemiologic data on the incidence and progression of DR. This information is important in medical counseling and for developing approaches to prevent DR. The purpose of the present study was to estimate the 4-year incidence of DR and to identify risk factors associated with retinopathy and its progression in type 2 diabetic patients.

METHODS

In this prospective study 120 diabetic patients without retinopathy diagnosed by history or fasting blood glucose according to the American Diabetes Association (ADA) criteria were selected consecutively.

Exclusion criteria were retinal vascular diseases, high myopia, chorioretinal degeneration, and history of retinal surgery.

Similar procedures were conducted at both the baseline and 4-year follow-up visits, including detailed interview by trained interviewers covering both ocular and systemic medical history and medication usage. All the patients were visited every year during this period by an ophthalmologist. Comprehensive eye examination and measurement of height, weight, and seated blood pressure (BP) were performed. Fasting blood test for blood glucose and serum lipids were done. All patients underwent an ophthalmic examination by an ophthalmologist including slit-lamp biomicroscopy and indirect ophthalmoscopy with dilated pupils. Best-corrected visual acuity (BCVA) was measured using the Snellen E chart.

We followed the Early Treatment of Diabetic Retinopathy Study (ETDRS) final scale criteria, to define presence of questionable diabetic retinopathy (6). As in the WESDR (7) the retinopathy level for each participant was derived by concatenating the levels for the two eyes, giving the eye with the higher level greater weight. This scheme provides a 15-step scale (10/10, 14–15/10, 14–15/14–15, 20/<20, 20/20, 35/<35, 35/35, 43/<43, 43/43, 47/<47, 47/47, 53/<53, 53/53, 60/<60, 60/60), with all levels of proliferative retinopathy grouped as one step. The higher level of retinopathy for the two eyes thus determines the level of retinopathy for each participant. For the purposes of this study, an increase of one or more steps on the 15-step scale over the 5-year period from the baseline examination was considered to indicate progression of retinopathy.

Informed consent was obtained from all subjects and the research had the approval of the institutional review board and ethics committee of the Yazd University of Medical Sciences and was carried out in accordance with the Declaration of Helsinki.

Statistical methods

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS version 12.0, Chicago, IL, USA). Chi-square test was used for risk analysis and Student *t*-test was used to compare discrete variables. Significance was considered to be $p<0.05$. Results are given with their 95% CIs. Data are presented as means ± SD.

RESULTS

In this study 120 patients with no retinopathy were selected. Patients (31 male, 89 female) were followed for 4 years. The mean age of these patients was 55.2±9.64 years and the mean duration of diabetes was 11.6±6.2 years. After 4 years, 57 patients were affected by retinopathy that was mild in 43 (35.8%) and 10 (8.3%) moderate, whereas 3 patients (2.5%) had severe NPDR. PDR was found in one patient (0.8%).

The 4-year cumulative incidence of DR was 47.5 % (38.6%–56.4% [95% CI]). The incidence of DR was 5.8% in the first year, 20.3% in the second year, 24.4% in the third year, and 7.4% in the fourth year (Tab. I, Fig. 1).

The mean age of patients without DR was 54±9.5 years and in patients with DR was 58.29±15.91 years, but this difference was not significant (p=0.07).

Patients with DR had worse glycemic control than patients with no retinopathy. The mean fasting blood sugar (FBS) in the DR group was 191.26±60.51 mg/dL but there was 185.76±60.22 mg/dL in patients without DR. The higher FBS was associated with higher DR grade. FBS was 189.86±57.55 mg/dL in mild NPDR, 170.9±50.99 mg/dL in moderate NPDR, and 296.33±35.64 mg/dL in severe NPDR (p=0.02) (Tab. II). There was no significant association between 2 h plasma glucose and DR (p=0.19).The diabetes duration was 9.8±4.5 years in no DR group, 12.4±7.2 in mild NPDR, 16.9±5.3 years in moderate NPDR, 20.0±8.0 years in severe NPDR (p<0.05). Systolic BP was significantly higher in DR group and the higher systolic BP associated with higher DR grade. In this manner the mean systolic BP was 126.19±12.97 mm Hg in no DR group, 133.09±16.3 mmHg in mild NPDR, 134.5±21.4 mm Hg in moderate NPDR, and 126.66±37.85 mm Hg in severe NPDR (p=0.004). This correlation was not seen for diastolic BP (p=0.98). The mean serum cholesterol was 195.35±95.56 mg/dL in DR group and 188.32±42.63 mg/dL in no DR group, but this was not significant (p=0.47) (Tab. II).

The incidence of DR in patients with FBS≥140 mg/dL was 50% and in FBS <140 mg/dL was 39.2%. The risk of DR in the first group was 1.27 times more than the second group but this correlation was not significant (p>0.05).The risk of DR in patients with 2 h PP ≥180 mg/dL was significantly (twofold) higher than 2 h PP <180 mg/dL (p<0.05) (Tab. III).

The incidence of DR in patients who received insulin was 71.4% but this figure was 46% in patients taking oral hypoglycemic agent (OHA). The risk in insulin group was 1.55 times more than oral hypoglycemic agent (OHA) (p>0.05).

The incidence of DR was 66.6% in smokers and 47% in nonsmokers. The risk of DR in the smoker group was 1.47 times more than nonsmokers (p>0.05).

The incidence of DR in hypertensive patients was 55.3% and in normotensive patients was 41%; the risk of DR was 1.37 times in first group compared to second group (p<0.05).

The risk of DR in men was 1.32 times more than women

TABLE I - YEARLY DIABETIC RETINOPATHY (DR) INCIDENCE ACCORDING TO TYPE OF RETINOPATHY

Year	No DR	Mild NPDR	Moderate NPDR	Severe NPDR	PDR
Year 0 (baseline)	120	0	0	0	0
Year 1	113	6	1	0	0
Year 2	90	17	5	1	0
Year 3	68	16	4	2	0
Year 4	63	4	0	0	1

NPDR = Nonproliferative DR; PDR = Proliferative DR

TABLE II - AVERAGE OF PONDERING VARIANT IN PERSONS WITH AND WITHOUT RETINOPATHY

	With retinopathy	Without retinopathy	p value
Age (year)	58.29 ± 15.91	54 ± 9.5	0.07
BMI (Kg/m^2)	26.72 ± 3.71	27.81 ± 4.39	0.14
Duration of diabetes (year)	13.7 ± 7.13	9.82 ± 4.52	0
FBS (mg/dL)	191.26 ± 60.51	185.76 ± 60.22	0.61
2 h PP (mg/dL)	303.26 ± 82.10	278.20 ± 83.48	0.1
TG (mg/dL)	220.15 ± 95.65	238.77 ± 133.74	0.38
Chol (mg/dL)	195.35 ± 44.56	188.32 ± 42.63	0.47
Systolic BP (mmHg)	133.83 ± 19.18	126.19 ± 12.97	0.01
Diastolic BP (mmHg)	81.6 ± 7	82.7 ± 21.9	0.73

BMI = Body mass index; FBS = Fasting blood sugar; TG = Triglycerides; BP = Blood pressure

but this association was not significant (58% vs 43.8%).The incidence of DR in patients with more than 10 years duration of diabetes was 56.9% but this figure was 36.3% in patients with less than 10 years duration. The risk of DR in the first group was 1.56 times more than second group ($p<0.05$) (Tab. III).

DISCUSSION

In this study 4-year cumulative incidence of DR was 47.5%: 35.8% for mild NPDR, 8.3% for moderate NPDR, 2.5% for severe NPDR, and 0.8% for PDR in type 2 diabetic patients who were free of DR in the beginning of the study.

The 4-year incidence and progression of retinopathy were investigated by Wisconsin Epidemiologic Study of DR (WESDR) in people with diabetes diagnosed at 30 years of age or older. For insulin users, 73 (47%) of the 154 who did not have any retinopathy at the first visit developed it in the 4-year interval. For nonusers of insulin, corresponding rates were 34% (110/320) for incidence of any retinopathy (5), which was similar to our study.

In Kim et al's study of 130 patients who were free of DR at baseline, 30 developed it, giving an incidence of 44.4/1000 person-years. Age and known duration of diabetes, mean fasting plasma glucose, and HbA1C levels during the follow-up period were higher in the patients who developed DR. This study concluded that poor glycemic control is the most important risk factor for both the development and progression of DR in NIDDM patients (8). In United Kingdom Prospective Diabetes Study (UKPDS), of the 1919 patients, 1216 (63%) had no retinopathy at diagnosis. By 6 years, 22% of these pa-

TABLE III - RELATIVE RISK OF DIABETIC RETINOPATHY (DR) ACCORDING TO EVALUATED RISK FACTORS

		No DR	DR	Incidence	Risk	CI	p value
Diabetes duration	10 y and more	28	37	56.9	1.56	1.04–2.36	<0.05
	Less than 10 y	35	20	36.3		2.36	
FBS (mg/dL)	140 and more	46	46	50	1.27	0.76–2.11	>0.05
	Less than 140	17	11	39.2		2.11	
TG (mg/dL)	150 and more	50	44	46.8	0.93	0.6–1.4	>0.05
	Less than 150	13	13	50		1.4	
Medicine	Insulin	2	5	74.1	1.44	0.86–2.3	>0.05
	Oral	52	51	49		2.3	
Smoking	Smoker	1	2	66.6	1.41	0.62–3.23	>0.05
	Nonsmoker	62	55	47		3.23	
2 h PP (mg/dL)	180 and more	57	57	50	2	1.66–2.4	<0.05
	Less than 180	6	0	0		2.4	
Systolic BP (mmHg)	130 and more	35	35	50	1.16	0.78–1.73	>0.05
	Less than 130	28	21	42.8		1.73	
Diastolic BP (mmHg)	85 and more	11	16	59.2	1.36	0.92–2.01	>0.05
	Less than 85	52	40	34.4		2.01	
Gender	Male	13	18	58	1.32	9.0–1.9	>0.05
	Female	50	39	43.8		1.9	
BMI (Kg/m^2)	25 and more	50	38	43.1	0.72	0.5–1.05	>0.05
	Less than 25	13	19	59.3		1.05	

FBS = Fasting blood sugar; TG = Triglycerides; BP = Blood pressure; BMI = Body mass index

tients had developed retinopathy that was microaneurysms in both eyes and worse. Development of retinopathy was strongly associated with baseline glycemia, glycemic exposure over 6 years, higher BP, and without smoking (9).

Looker et al indicated that diabetes duration, hyperglycemia, the type of treatment for diabetes (insulin use HRR, 3.06 and oral hypoglycemic use HRR, 2.40 compared with individuals on no pharmacotherapy), and microalbuminuria were associated with the development of retinopathy (10). In our study there was no significant association between type of treatment and DR incidence.

Yoshida et al investigated the risk factors for development of DR in 787 type 2 diabetic patients with no DR at the first visit. The subjects were followed up for at least 3 years. Among the baseline factors, significant correlations were observed between the development of DR and HbA1c, the method of therapy, the duration of diabetes at the first visit, and the past maximal body mass index (BMI). No significant correlation was found with the BP, age, gender, total cholesterol, or BMI. Among the follow-up variables, the mean HbA1C and duration of diabetes correlated significantly with DR development, whereas the BP and age did not. They found that a 1% decrease in HbA1c led to a 35% reduction in the risk of development of DR during the follow-up (11). Among Pima Indians with Type 2 diabetes mellitus in the cross-sectional analysis, HbA1c, fasting, and 2 h plasma glucose were each significantly related to retinopathy among 789 diabetic subjects by separate logistic models. In this study HbA1C was selected as having the strongest association with retinopathy and neither fasting nor 2 h plasma glucose contributed significantly to the model once HbA1C was entered (12). One of the limitations in our study was lack of HbA1C measurement.

In Moss et al's study, after controlling for known risk factors for the incidence and progression of DR, pack-years smoked was borderline significant in predicting incidence of DR in younger-onset subjects. Smoking was not associated with incidence of DR in older-onset subjects or with progression to PDR in any of the groups (13). Although in our study the incidence of DR in smoker subjects was 1.41 times more than in nonsmokers, this correlation was not significant.

In some studies DR progression was seen after intensive glycemic control. In DCCT study, the long-term benefits of intensive insulin treatment greatly outweighed the risks of early worsening (14). In Agardh et al's study in patients treated with oral drugs at baseline, the incidence of any type of retinopathy was 30.8% and of severe DR 5.7%. In patients treated with insulin at baseline, the incidence of any type of DR was 41.0% and of severe DR 16.1% (15). Our results showed that incidence of DR in insulin group was 71.4% and in oral hypoglycemic agent group was 46%.

In a 10-year clinic-based study (16), 833 type 2 diabetic patients were studied. Of the patients without retinopathy at the age of 50, 10% developed retinopathy during 4 years of follow-up. These patients had longer duration and younger onset of diabetes than the group without retinopathy at the 4-year follow-up. Teuscher et al showed that there was a statistically significance relation between FBS, SBP, insulin therapy, and incidence of DR (17), which was similar to our results.

In a study was performed in Pima Indians, there was no significant association between BP and incidence of DR (18). In our study increased systolic BP was associated with increased risk of incidence and progression of DR. In another study in Pima Indians, incidence of DR was strongly related to insulin treatment, disease duration, plasma glucose concentration, and presence of other complications (19). In our study the incidence of DR in patients taking oral hypoglycemic agent and SBP >130 mmHg was 52% and in patients with SBP <130 mmHg 43%.The Blue Mountains Eye Study examined 3654 residents aged 49 years or older at baseline. The cumulative 5-year incidence of DR was 22.2%. This study concluded that increase in diabetes duration and elevated baseline fasting blood glucose level predicted retinopathy incidence (20).

Some affecting factors in DR incidence are preventable but some of them cannot be changed. Controlling some factors like blood glucose, BP, using new treatment, and lifestyle intervention can decrease incidence of DR. One of the factors investigated less in epidemiologic study is lifestyle intervention. Lifestyle role in incidence of DR should be evaluated carefully in further studies.

CONCLUSIONS

The cumulative incidence after 4-year follow up in type 2 diabetic patients older than 30 years was 47.5%, which shows the importance of this problem. As higher baseline fasting blood glucose levels, longer duration of diabetes, and higher systolic BP were the only statisti-

cally significant risk factors found for retinopathy progression after 4 years in this study, contributing factor management and long care improvement are needed to solve this problem.

Proprietary interest: None.

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