

# A Delayed Diagnosis in Type 2 Diabetes: Retinopathy

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Diabetic retinopathy is the leading cause of blindness in the 20-74 years old age group in developed countries. Aim of this retrospective study was to evaluate the incidence of diabetic retinopathy (DR) and the general characteristics of the patients in their first admittance to the Şişli Etfal Hospital Diabetes Center. A group of 1181 patients diagnosed as type 2 diabetes mellitus according to the WHO criteria admitting to Şişli Etfal Hospital Diabetes Center for the first time in years 2000 or 2001 were studied retrospectively. Retinal examination was performed on all patients by the ophthalmology clinic in the first admittance and was repeated annually. Diabetic retinopathy was diagnosed in 268 (22.69%) of the 1181 retrospectively studied patients. 151 (56.00%) of these cases were evaluated as background DR (mild-moderate nonproliferative), 61 (23.11%) as preproliferative DR (moderate-advanced nonproliferative) and 56 (20.89%) as proliferative DR. In the retinopathic patient group, mean value for age was 59.11±11.46 years, Hb A<sub>1c</sub> 9.31±2.30%, fasting blood glucose 219.49±87.04 mg/dL, duration of diabetes 10.20±7.59 years, age of onset of diabetes 49.02±12.19 years. Microalbuminuria was detected in 150 of the 268 cases and ≥30 mg/day microalbuminuria was reported in 80 patients. Mean amount of microalbuminuria in these 80 patients was 263.97±67.9 mg/day. Risk factors known to be responsible for the development of DR such as chronic hyperglycemia, accompanying hypertension, dyslipidemia, diabetic nephropathy and diabetes duration was observed by the evaluation of the general characteristics of the patient group. A DR rate of 23% at first admission suggests that the health care personnel as well as the patient population are ignorant about the management of diabetes mellitus and its complications.

**Key words:** Diabetic retinopathy, type 2 diabetes mellitus

## Introduction

In the developed countries DR is estimated to be the most frequent cause of new cases of blindness in the 20-74 years age group. Blindness due to diabetic retinopathy is generally caused by nonresolving vitreous hemorrhage, traction retinal detachment or diabetic macular edema (1).

Prevalence of DR increases directly proportional to the duration of diabetes (3). DR is present in 20% of the patients with type 2 diabetes at the time of diagnosis, but the rate is as high as 60-85% after 15 years. Proliferative DR (PDR) is observed in 3-4% of patients with duration of diabetes <4 years and 5-20% of patients with >15 years of type 2 diabetes (2). According to the Wisconsin group, DR develops in 34% of the patients with type 2 diabetes within 4 years. In the 10 year follow-up 25% of DR patients showed progression and 2% developed PDR. Macular edema is observed at a rate of 3% in the initial nonproliferative phase, 38% in the moderate nonproliferative phase and 71% in the proliferative retinopathy phase (3). The

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study by Klein reports the rate of retinopathy in type 2 diabetics in the 10 years term to be 67%. In the type 2 diabetic group without initial proliferative retinopathy, progression was observed in 53% of the cases (4). Diabetic retinopathy study claims that with strict follow-up and treatment, blindness due to diabetes can be decreased as much as 98%. Unfortunately only 45% of the patients can access sufficient ophthalmologic examination and treatment (5). According to the results of the Diabetes Control and Complications Trial (DCTT), a 1% decrease in the HbA<sub>1c</sub> level decreases the risk of development of diabetic retinopathy by 69% and progression of the disease and necessity of fotocoagulation by 56%. Diabcare Program, declared in Saint Vincent in 1989, aims to decrease the incidence of blindness due to diabetes by 1/3 (5).

Because even the high-risk lesions may be asymptomatic, routine ophthalmologic examination of the diabetic patients is of utmost importance. Being both an important health issue that can be recognized at the latent or early stage and providing the chance of treatment in the diagnosed cases, diabetic retinopathy is a condition suitable for screening programs (2).

## Material and Methods

1181 patients admitting to Şişli Etfal Hospital Diabetes Clinic for the first time between January 2000 and June 2001 with previous diagnosis of or newly diagnosed type 2 diabetes according to WHO criteria are sent to the ophthalmology clinic of the same hospital for routine dilated eye examination

and 268 cases with the diagnosis of retinopathy are included in the study group.

All of the cases have undergone routine ophthalmologic examination which included visual acuity assesment, biomicroscopy, tonometer and fundus examination. Fundus examination is performed with binocular indirect ophthalmoscope, 78 diopter lens, Goldman 3 mirror contact lens and contact lens biomicroscope methods. Fundus flourescein angiography is performed whenever necessary. Follow-up of the patients evaluated as retinopathic were performed by the retina unit of the ophthalmology clinic.

Sociodemographic aspects and metabolic records of the cases are studied retrospectively from the files of the diabetes unit. Statistical analysis were performed by SPSS 9.0 statistical programme. Levels of significance were tested by using student t-test or for multiple comparisions one-way ANOVA with Fisher's test and for correlation spearman frank correlation coefficients were calculated.

## Results

Retinopathy was present in 268 (22.69%) of the 1181 retrospectively studied patients. In the nonretinopathic patient group mean fasting blood glucose was 162.00±41.12 mg/dl, systolic blood pressure 145.64±23.24 mmHg, total cholesterol 198.62±41.24 mg/dl, triglyceride 162.24±41.32 mg/dl and HDL was 48.12±12.31 mg/dl. Those values are significantly lower than retinopathic group (p<0.001). Socio-demographic characteristics of the two groups are summarized in Table 1.

**Table 1.** Sociodemographic characteristics of the retinopathic and nonretinopathic patients

	retinopathic		nonretinopathic		Student t-test
n	268		913		
Age (years)	59.11±11.46		62.51±10.86		P<0.05
Duration of diabetes (years)	10.20±7.59		7.11±2.75		P<0.001
Age of onset of diabetes (years)	49.02±12.19		56.42±16.14		P<0.001
HbA <sub>1c</sub> (%)	9.31±2.3		7.84±1.7		P<0.001
Chronic complications	n	%	n	%	
Nephropathy (microalbuminuria ≥30 mg/day) (150 cases)	80	53.3	278	25	P<0.001
Diabetic foot	14	5.5	10	1.2	P<0.001
Hypertension	129	48.13	301	32	P<0.001
Hyperlipidemia	156	58.2	331	34	P<0.001

**Table 2.** General characteristics of the cases according to the stage of retinopathy

	Background DR (mild nonproliferative)	Preproliferative DR (moderate nonproliferative)	Proliferative DR	ANOVA
n	151	61	56	
%	56	23.11	20.89	
Age of onset of diabetes (years)	51.57±11.59	46.02±11.30	45.30±12.89	0.002
Duration of diabetes (years)	7.97±6.42	12.14±8.5	14.42±7.17	0.000
Fasting blood glucose (mg/dL)	214.06±89.15	239.6±86.96	211.77±82.0	NS
HbA <sub>1c</sub> (%)	9.29±2.46	9.64±2.39	8.86±1.75	NS
Microalbuminuria (mg/day)	187.1±53.6	225.97±52.9	368.98±57.9	0.000
Systolic blood pressure (mmHg)	148.6±26.8	145.3±24.0	148.9±24.8	NS
Diastolic blood pressure (mmHg)	87.0±16.3	83.4±14.9	83.4±13.0	NS
Total cholesterol (mg/dL)	214.8±46.9	212.6±45.0	216.1±51.3	NS
Triglyceride (mg/dL)	190.4±11.5	146.7±9.2	167.1±11.9	NS
HDL (mg/dL)	46.7±13.1	50.3±14.4	46.6±13.3	NS

When the retinopathic group is compared with nonretinopathic group, duration of diabetes, age of onset of diabetes, HbA<sub>1c</sub> level and the percentage of diabetic complications were significantly higher in the retinopathic group. Especially mean amount of microalbuminuria (122.11±11.21 vs 263.97±67.90 mg/day) in nonretinopathic group was found to be low significantly ( $p < 0.001$ ).

Diabetes duration, level of metabolic control, the age of onset of diabetes all displayed positive correlation with diabetic retinopathy ( $r = 0.67$ ,  $r = 0.59$ ,  $r = 0.49$ , respectively,  $p < 0.001$  for all). Multiple regression analyses showed that diabetes duration and the level of metabolic control were independent variables of diabetic retinopathy ( $r = 0.61$ ,  $p = 0.000$ ,  $r = 0.57$ ,  $p = 0.000$ , respectively).

Table 2 summarizes the data obtained by classifying the 268 diabetic retinopathy cases according to the stage of retinopathy.

Family history revealed 55 (20.8%) patients to have mothers, 31 (11.8%) to have fathers, and 97 (30.4%) to have brothers or sisters as being the only diabetic member of the family; both parents of the patient were diabetic in 11 (4.1%) cases and 91 (29.3%) patients had second degree diabetic relatives.

## Discussion

The incidence of retinopathy in the type 2 diabetic study group with a mean duration of diabetes of 10.2±7.59 years was found to be 23%; the incidence

corresponds to the results of the reported studies (1,3,4). Chronic hyperglycemia, type and duration of diabetes, puberty, accompanying hypertension, hyperlipidemia, diabetic nephropathy, pregnancy and genetic factors are among the risk factors for diabetic retinopathy, as reported by epidemiologic studies (3,4,6).

Diabetic retinopathy generally does not show any symptoms in the early stages of the disease (7). This may cause problems for the doctors inexperienced in the field to diagnose diabetic retinopathy in the early stages despite the utilization of direct or indirect ophthalmoscope. Federman et al reported in their study that 52% of internists, 33% of diabetologists and 9% of ophthalmologists failed to diagnose PDR in diabetic patients (15).

Elevated glycosylated hemoglobin levels are among the most important risk factors for the development of diabetic retinopathy. It was reported that in the insulin dependent diabetic cases microalbuminuria rises 3.6 fold and retinopathy rises 2.5 fold in the patient group whose HbA<sub>1c</sub> levels are 1.5 times the normal value when compared with the non-microalbuminuric group (11,12). DCTT report claims that lowering HbA<sub>1c</sub> level by 1% causes a 69% decrease in the chance of retinopathy development (5).

Mean HbA<sub>1c</sub> level in retinopathic group was 9.31±2.30%, and it was above the acceptable upper limit of 7%, whereas 7.84±1.70% in nonretinopathic group. Multiple regression analyses showed that

poor glycemic control was independent risk factor for diabetic retinopathy, although no significant difference between HbA<sub>1c</sub> levels of retinopathy stage groups were observed when the groups were compared (p=NS).

Another risk factor for diabetic retinopathy is the duration of diabetes (7). According to the Wisconsin epidemiologic study, risk of diabetic retinopathy in insulin dependent diabetes with age of onset before 30 years is 59% in 4 years, 74% in 10 years and 97% in 20 years. Rate of diabetic retinopathy development in insulin dependent diabetes with age of onset after 30 years is reported by the same study to be 47% in 4 years and 34% in 10 years (3,4).

Incidence of retinopathy in patients with duration of diabetes  $\geq 15$  years is found to be 6 times higher than the group with duration of diabetes  $< 4$  years by the diabetic retinopathy study performed by Leyla Atmaca et al on a group of 2318 type 2 diabetic patients (16). Mean duration of diabetes in our study group is  $10.2 \pm 7.59$  years and is compatible with the records from previous studies. When the study group is classified according to the stage of retinopathy, mean duration of diabetes for the background diabetic retinopathy group is  $7.97 \pm 6.4$  years and duration of diabetes increases directly proportional to the stage of retinopathy to be as high as  $14.42 \pm 7.17$  years for the proliferative group (p=0.000).

Hypertension is another risk factor for diabetic retinopathy. Incidence of diabetic retinopathy is reported to be higher in hypertensive and nephropathic type 2 diabetes mellitus patients when compared with the group without these complications (9,11, 12). Mean systolic blood pressure for the overall study group is  $147.97 \pm 25.69$  mmHg and this value is high above the normotensive limit for diabetic patients, which is 135 mmHg. Comparison of the mean systolic blood pressures in the subgroups based on the stage of retinopathy did not reveal statistically significant differences, nevertheless all subgroups were found to be hypertensive.

It is suggested that diabetic nephropathy, another microangiopathic complication of diabetes, increases the risk of diabetic retinopathy development by elevating the blood pressure and the serum level of fibrinogen. Plasma prorenin level is also found to be associated with the development of diabetic

retinopathy and nephropathy (10,12-14). Microalbuminuria levels measured concurrently with retina examination are present in 150 of the 268 cases and microalbuminuria level is found to be  $\geq 30$  mg/day for 80 patients. Mean microalbuminuria value for these 80 patients was  $263.97 \pm 67.9$  mg/day. Comparison between microalbuminuria positive and microalbuminuria negative groups showed that incidence of proliferative diabetic retinopathy is significantly higher in the patients with microalbuminuria than the others (p=0.001). When the groups based on the stage of retinopathy are compared, mean microalbuminuria level in the background retinopathy group is the lowest while the values in the proliferative group were beyond macroalbuminuric levels and this difference is found to be statistically significant (p=0.000).

In patients with diabetic retinopathy, elevations in serum lipid levels increase the risk of developing hard exudates. Number of retinal hard exudates is directly proportional to the risk of blindness. Decreases in serum lipid levels is reported to be associated with decreases in cardiovascular mortality and development of hard exudates (9,13,15). Mean total cholesterol and triglyceride levels of the 268 retinopathic patients were above the acceptable levels for diabetics. Comparison of the groups based on the stage of retinopathy showed the mean total cholesterol and triglyceride levels for the patients with maculopathy to be higher than other groups, even though this difference did not show statistical significance.

Effect of genetic factors on development of diabetic retinopathy is currently being investigated. It has been suggested that cases with HLA DR4 and DR3 phenotype show increased risk of developing diabetic retinopathy (17). A notable prominence of first and second degree diabetic relatives was observed when the family history of the patient group was studied.

An incidence of 23% at first admission approves the fact that diabetic retinopathy, the leading cause of preventable blindness, is ignored by both the patient population and the healthcare personnel. Age of onset of diabetes, duration of diabetes, chronic hyperglycemia, accompanying hypertension, dyslipidemia, diabetic nephropathy and positive family history are among the risk factors for the development of diabetic retinopathy.

In conclusion, routine retinal examination is crucial for the diagnosis and follow-up of diabetic retinopathy. Treatment of the patient group carrying the greatest risk for this complication will lead to major reductions in the expenses that will arise due to blindness. Chronic hyperglycemia, hypertension and dyslipidemia are among the preventable risk factors of diabetic retinopathy. Regulation of blood glucose and effective treatment of hypertension and dyslipidemia may prevent the development of diabetic retinopathy and slow down the progression of this complication.

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