PREVALENCE OF RETINOPATHY AND ITS RELATION WITH VARIOUS RISK FACTORS IN TYPE 1 DIABETES MELLITUS – HOSPITAL BASED STUDY

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ABSTRACT

The aim of this study was to estimate the prevalence of retinopathy in type 1 diabetes mellitus and to correlate it with various risk factors, age of onset, duration of diabetes, dyslipidemia, microalbuminuria and other complications of diabetes. 100 patients of type 1 diabetes mellitus, who were randomly selected, were included in this study. All patients were subjected to detailed clinical and biochemical examinations. Fundus examination was done by direct ophthalmoscopic examination and by taking 30° non-stereoscopic retinal photographs. Retinopathy was classified by EURODIAB – Hammersmith grading system. The study group was divided into group A- those with retinopathy and group B- those without retinopathy. Statistical analysis was done by Chi Square and unpaired student's "t" test. Association with various factors were analysed by logistic regression model. Out of 100 patients of type 1 diabetes, 25 patients had retinopathy. Mean age of group A was 31.4 $\pm$ 10.9 years, while in the control group it was 27.0 $\pm$ 7.5 years. Statistically significant association was observed in duration of diabetes (χ^2: 76.366; P<0.001), BMI (χ^2 = 6.582; P<0.05) glycemic control (FBS in group A: 184.9 $\pm$ 103.5 mg/dl; In group B: 170.0 $\pm$ 90.1mg/dl and GHb in group A 9.69 $\pm$ 2.07%, group B: 9.12 $\pm$ 1.7%, p value <0.01 and 0.001 respectively) lipid profile (P:<0.001) and microalbuminuria (χ^2 = 14.012; P<0.001). The prevalence of retinopathy in type 1 diabetes mellitus was found to be 25%. There was very strong association between the prevalence of retinopathy and duration of diabetes, BMI, glycemic control, microalbuminuria and dyslipidemia.

INTRODUCTION

Diabetic retinopathy leading to blindness is one of the most tragic complications of diabetes mellitus. Although retinopathy occurs in majority of patients with type 1 diabetes mellitus, the roles of several key risk factors are still poorly understood. Persistent hyperglycemia has been a major factor influencing the course and complications of diabetes, but it is not the only factor.

Several studies have been conducted to find out the prevalence of retinopathy in type 1 diabetes mellitus. In some of these studies association between various factors (viz. glycemic control, dyslipidemia, microalbuminuria, age of onset, duration of diabetes) and diabetic retinopathy was evaluated (1). The Diabetes Control and Complications Trial (DCCT), demonstrated a reduction in the development and progression of retinopathy in patients of IDDM with intensive therapy aimed at achieving glycemic control as close to the non diabetic range as possible (2). In the present study, we estimated the prevalence of retinopathy in a selected group of type 1 diabetics and tried to evaluate the role of various risk factors in precipitating retinopathy.

MATERIAL AND METHODS

The present study was a hospital based, randomized, case control study. Informed consent was taken from all patients after explaining the whole procedure and the motive of the study. The patients were divided into group A – those with retinopathy and group B – those without retinopathy.

A detailed history of each patient was obtained regarding the age, year of diagnosis of diabetes, age at onset and duration of diabetes, family history of diabetes, history of smoking and of any associated illness. Measurements to calculate BMI and W/H ratio were taken. Status of glycemic control was estimated by measuring glycosylated hemoglobin (GHb) by "Ion exchange resin method" with GHb kit. Serum triglyceride, HDL cholesterol and total cholesterol were estimated using an enzymatic kit on semi autonalyser.

Early nephropathy was established by the presence of microalbuminuria (Micral test) in at least two of the three tested samples. Overt nephropathy

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was confirmed by estimation of blood urea and serum creatinine by standard laboratory method. Neuropathy was evaluated by history of numbness, tingling sensation, pinprick sensation, paraesthesias or weakness and confirmed by detailed neurological examination, that included touch sensation by 10 g monofilament, vibration sense and ankle reflex. Patients suffering from diseases like Eales disease, sickle cell anemia, hyperviscosity syndrome, or any other condition that could cause retinopathy and patients not willing to cooperate were excluded from the study.

Retinopathy was evaluated after full dilatation of both the pupils by instillation of a topical mydriatic (0.5% tropicamide with phenylephrine), first by direct ophthalmoscopic examination of the fundus using beta 200 and beta 200 m2 direct ophthalmoscope and then by taking 30°, non-stereoscopic retinal photographs of each patient using the non-stereoscopic fundus camera, in a dark, quiet room with the patient seated comfortably. Each eye of the patient was photographed separately. Two precisely defined fields (disc-macula-temporal and disc-nasal) were photographed in each eye of the patient and the photographs were developed to 5 x 3 inch size. Retinopathy was considered to be present if red dots (microaneurysms or dot haemorrhage), red streaks (nerve fibre layer haemorrhages), hard exudates, soft exudates, edema, microinfarcts, intra retinal microvascular abnormalities, neovascularization or vitreous haemorrhage was present in either eye. Retinopathy was classified according to EURODIAB – Hammersmith grading system (3,4).

Statistical Analysis: For Chi Square test (χ^2), the Chi Square value was compared with the value of 5.99. χ^2 at 2df. If the value was >5.99, it was significant. The associations with various risk factors were tested using student's unpaired "t" test. The independent relation of duration of the disease, GHb and microalbuminuria to diabetic retinopathy were examined by logistic regression model.

RESULTS

Out of 100 patients of type 1 diabetes mellitus, 25 patients had retinopathy when their fundus was examined by direct opthalmoscopy and fundus photography by the non-stereoscopic fundus camera. Out of these 21 (84%) had non-proliferative, 3 (12%) had pre proliferative and only 1 (4%) had proliferative retinopathy. Clinical and epidemiological characteristics of the study population are shown in Table 1, Fig 1a and 1b.

In group A, the mean age of onset of diabetes was 23.6 ± 7.9 years, while in the control group B, it was 23.4 ± 7.3 years. The difference between the two groups was statistically insignificant. The mean duration of diabetes in the A group was 15.6 ± 5.3 years, while the mean duration of diabetes in group B was 3.7 ± 3.5 years. The difference between the two groups was found to be statistically significant (Table-2). Out of 25 patients of type 1 diabetes who had retinopathy, 3 (12%) were smokers and out of 75 patients who had no retinopathy 12 (16%) were smokers. The difference between the two groups was statistically insignificant. In the case group the mean BMI was 20.46 ± 4.66 kg/m^2 while it was 18.29 ± 2.55 in the control group. The difference between the two groups was found to be statistically significant (Fig-2).

Table 1: Clinical and Epidemiological Characteristics of the Study Population.

Characteristics	Patients with retinopathy		Patients without retinopathy		t	P#
	Mean	SD	Mean	SD		
Number (n=100)	25 (25%)		75 (75%)			
Age (Years)	31.4	10.9	30.2	9.3	0.565	NS
Sex (M/F)	15:1		47:3		0.00*	NS
Age at onset (years)	23.6	7.9	23.4	7.3	0.184	NS
Diabetic duration (Years)	15.7	5.3	3.7	3.5	4.858	0.03
Family history	11:1		14:6			
Smoking	3 (12.0%)		12 (16.0%)		0.026*	NS
BMI (kg/m^2)	20.46	4.66	18.29	2.55	9.495	0.003
W/H ratio	0.916	0.244	0.865	0.177	0.189	NS
Fasting blood sugar (mg/dl)	184.9	103.5	169.7	90.1	0.289	NS
GHb (%)	9.69	2.07	9.12	1.75	0.937	NS

** Value calculated by χ^2 test. # p calculated by unpaired student's test.*

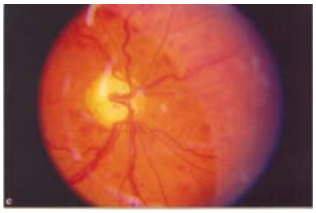


Fig 1a: Background Diabetic Retinopathy

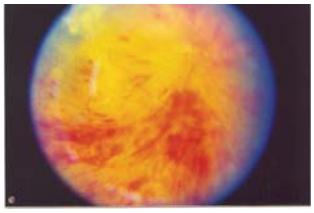


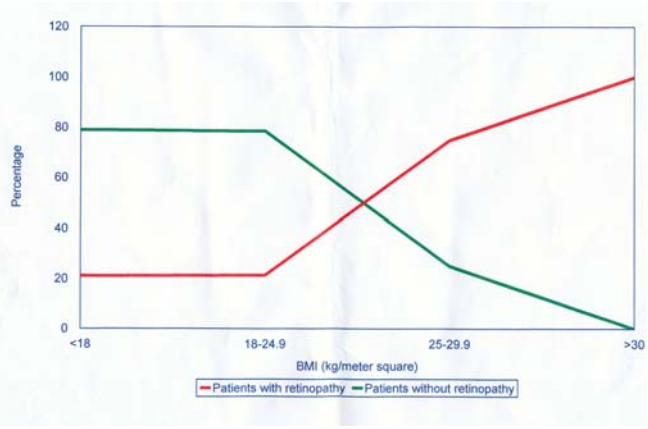
Fig 1b: Proliferative Retinopathy

Table 2: Relation of Retinopathy with Duration of Diabetes

Duration of Diabetes (yrs)	n	Patients With Retinopathy	Patients without retinopathy	χ^2
< 5	51	0	51 (100%)	32.026
6-10	20	1 (5%)	19 (95%)	4.083
11-15	14	9 (64.3%)	5 (35.7%)	9.776
16-20	9	9 (100%)	0	18.286
21-25	5	5 (100%)	0	11.859
26-30	0	0	0	0
> 30	1	1 (100%)	0	0.336
Total	100	25	75	76.366

*(χ^2=76.366;p<0.001**)*

Fig: 2. Relationship of Retinopathy with BMI



The mean waist hip ratio in the case group was found to be 0.916 ± 0.244 while that in the control group was found to be 0.865 ± 0.177. The difference between the two groups was statistically insignificant (Fig-3). There were 62 males in the study, out of which 24.2% had evidence of retinopathy and 75.8% had no retinopathy. Amongst the 38 females, 26.3%

Fig: 2. Relationship of Retinopathy with Waist Hip Ratio

Table 3: Relationship of Retinopathy with Glycosylated Hemoglobin

GHb%	n	Retinopathy		χ^2
		Positive	Negative	
< 8	26	2(7.69%)	24(92.31%)	4.435
8.1-9	36	6(16.67%)	30(83.33%)	1.440
9.1-10	23	8(34.78%)	15(65.22%)	0.922
> 10	15	9(60.0%)	6(40.0%)	9.437
Total	100	25	75	16.234

*(χ^2= 16.234;p<0.001)**

Fig : 4. Relationship of Retinopathy with Fasting Blood Sugar

had retinopathy while 73.7% had no retinopathy. There was no statistically significant difference in the presence of retinopathy in the two genders (p value being >0.05). In the cases with retinopathy, 36% patients had neuropathy whereas in those without retinopathy, 17.3% patients had neuropathy. The difference between the two groups was statistically insignificant (p value >0.05). The mean value of fasting blood sugar in the case group was 184.9 ± 103.5 mg/dl while that in the control group was 169.7 ± 90.1 mg/dl. The difference between the two groups was statistically significant (p<0.01)(Fig-4). The mean glycosylated haemoglobin in patients of type 1 diabetes with retinopathy was 9.69 ± 2.07% while in the patient without retinopathy it was 9.12 ± 1.75%. The difference between the two groups was found to be statistically significant (p<0.001) (Table-3). The difference in microalbuminuria between groups with and without retinopathy was found to be highly significant (p<0.001) (Table-4). There was strong association of retinopathy and raised serum cholesterol (p<0.001), LDL cholesterol (p<0.001), Serum triglycerides (p<0.001) and VLDL cholesterol (p<0.001) and inverse relationship with HDL cholesterol (p<0.001) (Table-5). When multiple logistic analysis was used, duration of diabetes,

glycemic control and microalbuminuria were the strong predictors of diabetic retinopathy (Table-6).

Table 4: Relationship of Retinopathy with Microalbuminuria

Microalbuminuria mg/dl	Patients with retinopathy (n=75)		Patients without retinopathy (n=25)		x^2	P
	No.	%	No.	%		
< 20	6	24	55	73.33	17.16	< 0.001
20-50	11	44	17	22.67	3.24	> 0.05
50-100	8	32	3	4	12.29	< 0.001
> 100	0	0	0	0	-	-
Total	25	100	75	100	32.69	< 0.001

Table – 5: Relation of Retinopathy with Lipid Profile

Characteristics	Patients with retinopathy (n=25%)		Patients without Retinopathy (n=75)		x^2
	n	%	n	%	
Total Cholesterol (mg%)					
< 162	2	8	21	28	3.181
163-183	2	8	18	24	2.083
184-209	4	16	14	18.7	0.000
> 209	17	68	22	29.3	10.214
Total	25	100	75	100	15.478
LDL cholesterol (mg/dl)					
< 96	2	8	21	28	3.181
97-114	2	8	20	26.7	2.800
115-139	4	16	11	14.7	0.026
> 139	17	68	23	30.7	9.388
Total	25	100	75	100	15.369
HDL cholesterol (mg/dl)					
< 39	22	88	17	22.7	30.951
39-47	1	4	22	29.3	5.439
48-56	1	4	23	30.7	5.921
> 56	1	4	13	17.3	1.771
Total	25	100	75	100	44.082
Triglyceride (mg/dl)					
< 58	1	4	13	17.3	1.771
59-77	0	-	8	10.7	1.630
78-110	0	-	7	9.3	1.280
> 110	24	96	47	62.7	8.564
Total	25	100	75	100	13.245
VLDL cholesterol (mg/dl)					
< 20	1	4	26	34.7	7.458
21-30	7	28	31	41.3	0.905
31-40	3	12	17	22.7	0.750
> 40	14	56	1	1.3	39.767
Total	25	100	75	100	48.880

● *p value was highly significant in all characteristics i.e. < 0.001.*

Table 6: Multiple Logistic Regression Analysis of Selected Variables Found to be Predictive of Retinopathy

VARIABLES	ODD RATIO	95% CI
Duration of diabetes	115.58	21.58-618.94
GHb	5.44	1.55-19.18
Microalbuminuria	11.29	2.71-47.11
Multiple Factors	851	73.75-9819.15

DISCUSSION

In this study, on 100 patients of type 1 diabetes mellitus we observed the prevalence of retinopathy to be 25%. Agardh et al (5) estimated the incidence of retinopathy in type 1 diabetics to be 47.2%. Whereas Oslen et al (6) estimated the prevalence to be 60% in young Danish type 1 diabetics.

EURODIAB IDDM Complication study group (4) found the prevalence of background retinopathy to be 35.95% and that of proliferative retinopathy to be 10.3%. The probable explanation of low results of this study in comparison to other studies is due to a smaller cohort and inclusion of more fresh cases.

In this study, the mean duration of diabetes in the case group was 15.7 $\pm$ 5.3 years while that in the control group was 3.7 $\pm$ 3.5 years, rendering these results highly significant for the duration of diabetes. These findings are consistent with the findings of the DCCT (2). This trial demonstrated that the cumulative prevalence of retinopathy was less in patients with shorter duration of diabetes as compared to those with a longer duration. It also demonstrated that the average benefit of intensive therapy was affected by prior duration of IDDM i.e. shorter the duration, the greater is the impact of intensive therapy on the risk of retinopathy.

The relationship of retinopathy with the glycemic control was in concordance to those found in many other studies (7,8,9) including DCCT, however no safe glycemic level could be identified below which patients have no risk of developing retinopathy.

Klein et al (10), Danne et al (11), and various other studies showed a strong association between increasing severity of retinopathy and proteinuria. Similar association was found in this study. In microalbuminuria range of 20-50 mg/dl, there were

44% patients from the group with retinopathy as compared to 22.7% patients from the group without retinopathy, in the microalbuminuria range of 50-100 mg/dl there were 32% patients from the group with retinopathy which also included the sole patient in our study with proliferative retinopathy, while there were only 4% patients from the group without retinopathy.

The association found between retinopathy and lipid profile in our study was consistent with the findings of Miccoli et al (12) who observed raised level of total and LDL cholesterol and reduced level of HDL/LDL cholesterol ratio in patients with diabetic retinopathy. Similar results were observed by Gordon et al (13) and Chew et al (14). However, different observations were made by Agardh et al (5), who found no significant difference in the level of total cholesterol, triglycerides, HDL cholesterol and LDL cholesterol between patients with established proliferative retinopathy and patients without retinopathy.

There were 22 patients who had neuropathy out of which nine patients had retinopathy and 13 patients had no retinopathy. The relationship between retinopathy and neuropathy was found to be statistically insignificant (p value >0.05). These findings did not correlate with the findings of Hanna et al (15) who found a strong association between proliferative diabetic retinopathy and the presence of peripheral sensory neuropathy.

Patients of type 1 diabetes with longer duration of disease, higher glycosylated Hb and microalbuminuria were significantly more likely to develop retinopathy. Similar observations were also made by Ramachandran et al (16).

In conclusion, we observed the relation of retinopathy with certain parameters. However, a greater effort and a much larger study would be required to predict the safe glycemic level below which there is no risk of retinopathy in type 1 diabetes. Early detection and control of modifiable risk factors can lead to a reduction in the incidence of diabetic retinopathy in patients with type 1 diabetes mellitus. As these patients have an onset of diabetes in early part of their life, the prevention of retinopathy, would definitely affect their quality of life.

A careful management of risk factors such as by achieving euglycemia, control of the serum lipid levels, microalbuminuria and BMI can prevent/ postpone the development of retinopathy.

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