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Clinical spectrum of diabetic retinopathy and its correlation with risk factors

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Abstract
Objectives: To study the clinical spectrum of diabetic retinopathy and its correlation with its risk factors.
Material and Methods: A prospective, cross sectional and unmasked study was done in patients of diabetes mellitus presenting in OPD of RIO, PGIMS Rohtak. Total 60 patients were included in the study which were divided into 3 groups each of 20 patients, based on the duration of DM: Group A < 5 years, Group B 6-10 years and Group C > 10 years. Staging of retinopathy was done on the basis of International diabetic retinopathy and diabetic macular edema severity scale. Demographical factors like age and sex were correlated with duration of DM. Various clinical forms of diabetic retinopathy ranging from no apparent DR to severe NPDR to PDR were correlated to different laboratory parameters like degree of hyperglycemia, Hb, lipid profile, blood pressure, renal function tests to ascertain correlation between them.
Results: Total prevalence of diabetic retinopathy in our study was 56.66%. Males were at higher risk in comparison to females. In our study, duration of disease was found to be strongly associated with diabetic retinopathy and macular edema. Hyperglycemia as measured by FBS and HbA1c is found to be an important risk factor in diabetic retinopathy. Hypertension, hypertriglyceridemia, deranged RFT and anaemia is statistically associated with diabetic retinopathy and its severity.
Conclusion: Diabetic retinopathy is a leading cause of preventable blindness. Therefore early diagnosis, timely screening and control of diabetes mellitus is of utmost importance.

Keywords: Diabetes mellitus, diabetic retinopathy, hypertension

Introduction
Diabetes mellitus (DM) is characterized by chronic hyperglycemia secondary to insulin resistance or defect in insulin secretion leading to long term multi organ complications of eyes, kidneys, nerves and blood vessels of heart. A fasting plasma glucose of $\geq$ 7.0 mmol/l is usually diagnostic laboratory threshold for diabetes [1]. WHO defines two type of DM mainly: Type 1 and 2. Other types are relatively uncommon and include diabetes secondary to pancreatic diseases, gestational diabetes and diabetes occurring as a part of genetic syndrome [2]. The estimated prevalence of diabetes for all age groups worldwide was 6.45% in 2010 and 7.7% in 2030 [3]. The total number of people with diabetes worldwide is projected to double by 2030. By 2030, India, China and U.S.A are expected to have the most number of people with diabetes [4]. The main macrovascular diseases related to atherosclerosis of larger arteries are ischemic heart disease, stroke and peripheral vascular disease. Diabetes also damages the capillaries causing microangiopathy [5].
The ocular complications of diabetes include diabetic retinopathy, iris neovascularisation, glaucoma, cataract and microvascular abnormalities of optic nerve. The most frequent complication is diabetic retinopathy. Diabetic retinopathy is a retinal consequence of chronic progressive microvascular leakage and occlusion. It is first evident ophthalmoscopically as non-proliferative diabetic retinopathy (NPDR), which may evolve into proliferative diabetic retinopathy (PDR). Typically early NPDR lesions include microaneurysm, dot and blot or flame shaped haemorrhages. More advanced NPDR lesions include hard exudates, cotton wool spots or soft exudates, intraretinal microvascular abnormalities (IRMA) and venous beading. PDR is characterized by growth of abnormal new vessels and fibrous tissue in response to retinal ischemia and the subsequent development of pre-retinal or vitreous haemorrhage. If new vessels appear one or within one disc diameter of the margin, they are known as new vessels on the disc (NVD). In other locations, they are referred to as new vessels elsewhere (NVE).

(NVE). High risk characteristics of PDR are NVD ≥1/3 disc area, any NVD with vitreous or pre-retinal haemorrhage, NVE ≥1/2 disc area in extent associated with vitreous or pre-retinal haemorrhage or vitreous or pre-retinal haemorrhage obscuring ≥ 1 disc area [6].

Capillary leak in the macular or perimacular region results in retinal thickening or diabetic macular edema (DME), defined as thickening located within two disc diameters of the centre of the macula. When it is present within or close to the central macula, it is termed Clinically Significant Macular Edema (CSME). Diabetic retinopathy has a multifactorial pathogenesis, involving many pathways linked to glycemia like aldose reductase, protein glycation, protein kinase C activation, angiotensin enzyme expression and vascular endothelial growth factor (VEGF) expression.

Classification of Diabetic Retinopathy: Various types of classification system of diabetic retinopathy have been proposed. In September 2001, American Academy of Ophthalmology launched a consensus development project with the goal of developing a new clinical severity Scale for diabetic retinopathy [7].

International Clinical Diabetic Retinopathy Disease Severity Scale

Proposed disease severity	Finding upon dilated ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild NPDR	Microaneurysms only
Mild to moderate NPDR	More than just microaneurysms but less than severe NPDR
Severe NPDR	Any of following • More than 20 intraretinal hemorrhages in each of 4 quadrants • Definitive venous beading in 2+ quadrants • Prominent intraretinal microvascular abnormalities in 1+ quadrant and no signs of proliferative retinopathy
Proliferative DR	One of the following • Neovascularisation • Vitreous/pre retinal hemorrhage

Macular Edema

Absent	**No retinal thickening or hard exudates in posterior pole**
Present	Mild- some retinal thickening or hard exudates in posterior pole distant from the macula Moderate- retinal thickening or hard exudates approaching the centre of macula but not involving the centre Severe- retinal thickening or hard exudates involving the centre of macula.

Material and Methods

It was a prospective, cross sectional and unmasked study in which patients of diabetes mellitus presenting in OPD of RIO, PGIMS Rohtak were included. A total of 60 patients were included in the study which were divided into 3 groups, each of 20 patients, based on the duration of diabetes mellitus: Group A <5 years, Group B 6-10 years and Group C > 10 years. Staging of retinopathy was done on the basis of International diabetic retinopathy and diabetic macular edema severity scale. Patients were classified according to the grade of severity of diabetic retinopathy in worse eye. Demographical factors like age and sex were correlated with duration of diabetes mellitus. Various clinical forms of diabetic retinopathy were correlated to different laboratory parameters like degree of hyperglycemia, Hb, lipid profile, blood pressure and renal function tests to ascertain correlation between them.

Inclusion criteria

All patients with type 1 and type 2 diabetes mellitus and those who were physically fit to undergo fundus examination.

Exclusion criteria

1. Accelerated hypertension
2. Active systemic infection
3. Coexisting ocular diseases like uveitis
4. Opaque media
5. Retinal disorders like retinal vein occlusion
6. Recent ocular surgery <6 months
7. Allergy to fluorescein dye
8. HIV positive status
9. Subjects with mental disorders

A detailed history including type of diabetes, duration of diabetes, treatment taken and personal history was taken. Systemic history of hypertension, cardiovascular disease, peripheral vascular disease, multiple sclerosis and Parkinson's disease was taken.

Systemic examination

Blood pressure was measured in sitting position using standard sphygmomanometer preferably in right arm. Examination of all major systems including cardiovascular, respiratory, abdomen and central nervous system was done thoroughly.

Ocular examination

Best corrected visual acuity (BCVA) using Snellens chart was recorded. A detailed anterior segment examination was carried out by diffuse illumination and slit lamp examination. Intraocular pressure was measured using Goldmann applanation tonometer and gonioscopy was done using Goldmann's three mirror to assess the angle of anterior chamber. Dilated fundoscopy was done both with Indirect ophthalmoscopy using +20D convex lens and +78D slit lamp biomicroscopy. Optical coherence tomography scan was done to assess the macular thickness using OPTOVUE RTVue. Fundus fluoroscein angiography (FFA) and fundus photo was also done using ZEISS FF450 digital camera. FFA was done to assess the presence of collaterals, neovascularisation, extent of capillary non-perfusion area and presence of macular ischemia.

Laboratory Parameters

5 ml of fasting blood was collected under aseptic conditions from antecubital vein of subjects and measurement of following parameters were done in the Biochemistry and Pathology department of PGIMS Rohtak.

1. Systolic and diastolic BP
2. Hemoglobin
3. Glycosylated haemoglobin (HbA1C)
4. Blood sugar fasting and postprandial
5. Lipid profile
6. Renal function tests

Statistical Analysis

At the end of the study, data was analysed using SPSS version 17. The comparison of difference in the means was calculated by using Independent t-test, One way Analysis of Variance (ANOVA) for multi-group comparisons and Chi-square test. The mean values of laboratory parameters were then compared with each grade of diabetic retinopathy and its association was determined statistically. A p value of less than 0.05 was considered statistically significant.

Results

A total of 60 patients of diabetes mellitus were studied, which were divided into 3 groups, each of 20 patients based on duration of diabetes. In our study, mean age of patients in group A was 45.22±9.31 years, group B was 55.40±11.16 years and Group C was 54.65±8.74 years. Maximum number of patients in our study were in the age group of 55-65 years. This was similar to the mean age of patients in study conducted by Rashmeih [8] (57.4 years) and Niazi[9] (56.23 years).

Table 1: Mean age ±SD in patients of Group A, B and Group C

Group	No of patients	Age range	Mean±SD
A (<5 years)	20	25-65	45.22±9.31
B (6-10 years)	20	25-72	55.40±11.16
C (>10 years)	20	38-72	54.65±8.74

In our study, there were more number of males than females (32 males and 28 females). The distribution was in accordance to Raman Kutty [10] and Niazi MK [9].

Table 2: Sex wise distribution in Group A, B and C

Sex	Group A	Group B	Group C	Total	%
Male	10	11	11	32	53.3
Female	10	9	9	28	46.7
Total	20	20	20	60	100

In our study, 8.33% patients were of type 1 diabetes and 91.66% patients were of type 2 diabetes. Type 2 DM was found to be significantly more prevalent than type 2 DM. Total prevalence of diabetic retinopathy was 56.66% in our study. Prevalance of DR was more in males (55.88%) as compared to females (44.12%). It is comparable to studies conducted by Shrivas [11] and Niazi [9].

In our study, 4 (20%) patients of Group A had diabetic retinopathy, 13 (65%) patients of group B and 17 (85%) patients of group C had diabetic retinopathy indicating that duration of diabetes is strongly associated with diabetic retinopathy. The patients who had history of DM less than 5 years, frequency of retinopathy was 15%, while those who had history of DM for more than 10 years the frequency was 85%. The difference in prevalence of DR was statistically significant. This was similar to studies conducted by Niazi [9] and Dandona *et al.* [12]

In Group A, 2 (10%) patients had mild NPDR, 2 (10%) patients had moderate NPDR and 16 (80%) patients had no apparent diabetic retinopathy. In Group B, distribution of mild, mild to moderate, severe NPDR and PDR was 4 (20%), 2(10%), 4 (20%) and 3 (15%) respectively. 7 (35%) had no apparent DR. In group C, this distribution was 6 (30%), 2 (10%), 4(20%) and 5 (25%) respectively and 3(15%) patients had no apparent DR. Prevalence of macular edema in group A was 2(10%), group B was 7(35%) and group C was 9(45%). The prevalence of different types of diabetic retinopathy and macular edema amongst three groups was found to be statistically significant ($p<0.05$). This result correlated well with studies by Romero *et al.* [13] and Mohan VK [14].

Hyperglycemia as measured by fasting blood sugar and HbA1c is considered an important risk factor associated with DR and it was significantly associated with retinopathy in our study. Fasting blood sugar in patients with no apparent DR was 127.61±32.87 mg/dl, mild DR was 137.91±27.88 mg/dl, mild to moderate DR was 146.33±29.43 mg/dl, severe was 280.12±86.46 mg/dl, PDR was 188.54±mg/dl which was statistically significant ($p<0.001$). The glycosylated haemoglobin in patients with no apparent diabetic retinopathy was 7.44±2.11%, mild DR was 6.94±1.34%, mild to moderate DR was 8.7±1.67%, severe was 11.83±0.54%, PDR was 10.16±1.41% which was statistically significant with $p<0.001$. It was in accordance to Winconsin Epidemiological Study of Diabetic Retinopathy (WESDR) which found that risk of retinopathy is related to the control of blood glucose levels [15].

Systemic blood pressure (SBP) in patients with no apparent DR was 129.11±11.68 mmHg, mild DR was 133.16±20.92mmHg, mild to moderate Dr was 148.33±18.77 mmHg, severe was 157.13±16.65 mmHg, PDR was 150.5±9.8 mmHg which was statistically significant ($p<0.001$). These results were similar study conducted by Estacio [16] which found that blood pressure is a significant predictor of progression and severity of DR.

The serum triglycerides in patients with no apparent DR was 198.15±63.82 mg/dl, mild DR was 228.83±57.40 mg/dl, mild to moderate was 244.16±32.55 mg/dl, severe was 241.87±29.08 mg/dl and PDR was 256±37.80 mg/dl which was statistically significant ($p<0.001$). In present study, serum total cholesterol in patients with no apparent DR was 206.15±51.82 mg/dl, mild DR was 228.83±57.40 mg/dl, mild to moderate was 215.16±22.55 mg/dl, severe was 441.87±19.08 mg/dl and PDR was 266±47.80 mg/dl which was statistically significant ($p<0.001$). In our study, serum LDL in patients with no apparent DR was 156.15±1.82 mg/dl, mild DR was 181.83±7.40 mg/dl, mild to moderate was 180.16±2.55 mg/dl, severe was 189.87±9.08 mg/dl and PDR was 196±7.80 mg/dl which was statistically significant ($p<0.001$). The Hoorn Study, a large population based study to determine the potential risk factors for retinopathy in diabetic and non-diabetic individuals showed that severity of DR and hard exudates are related to elevated serum total and LDL cholesterol levels [17]. Serum HDL in patients with no apparent DR was 36.53±8.46 mg/dl, mild DR was 33.25±6.28 mg/dl, mild to moderate was 36.5±2.56 mg/dl, severe was 34.5±5.6 mg/dl, PDR was 35.5±2.44 mg/dl which was statistically not significant ($p>0.05$). The present study did not find a significant association between HDL levels and severity of DR. It was similar to UKPDS who did not find an association [18].

Serum urea in patients with no apparent DR was 36.61±3.82 mg/dl, mild DR was 28.83±7.40 mg/dl, mild to moderate was 36±2.55 mg/dl, severe was 61.87±9.08 mg/dl and PDR was 42.75±3.80 mg/dl which was statistically significant ($p<0.001$). The difference in mean values of no apparent, mild, mild to moderate, severe NPDR and PDR was significant. In present study, serum creatinine in patients with no apparent DR was 0.776±0.245 mg/dl, mild DR was 0.583±0.383 mg/dl, mild to moderate was 1.083±0.240 mg/dl, severe was 1.4±0.523 mg/dl and PDR was 1.16±0.302 mg/dl which was statistically significant ($p<0.001$). These findings correlate to study conducted by Nivedita *et al*. [19] and Haddad *et al*. [20] who found a significant association of serum urea and creatinine with severity of DR.

Haemoglobin in patients with no apparent DR was 12.39±0.82 mg/dl, mild DR was 9.83±1.06 mg/dl, mild to moderate was 11.03±0.55 mg/dl, severe was 13.87±0.08 mg/dl and PDR was 12.36±0.80 mg/dl which was statistically not significant ($p>0.05$). The difference in mean values of no apparent, mild, mild to moderate, severe NPDR and PDR was not significant.

Conclusion

It is concluded that prevalence of DR was 56.66% which is significantly higher than found in other population based studies from southern India. This could be due to small skewed population studied by us which included referred patients from diabetic clinic and not patients from general population. This difference in prevalence can also be due to poor control of DM in our region. This study has provided us a clue to the burden of this sight threatening disease and an insight to the associated side factors with DR. In our study, duration of disease was found to be strongly associated with diabetic retinopathy and macular edema. Hyperglycemia as measured by FBS and HbA1c is found to be an important risk factor in diabetic retinopathy. Hypertension, hypertriglyceridemia, deranged RFT and anemia is statistically associated with diabetic retinopathy and its severity. Diabetic retinopathy is a leading cause of preventable blindness. Therefore early diagnosis, timely screening and control of diabetes mellitus is of utmost importance.

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