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# Prevalence of Diabetic Retinopathy and its Association with HbA1C, Autonomic Neuropathy and Microalbuminuria in Diabetic Patients of more than 5 Years Duration

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**Abstract**

**Introduction:** Ophthalmic complications are commonly seen in patients with long standing diabetes mellitus. The most severe manifestation, Diabetic retinopathy, is usually associated with raised HbA1C, autonomic neuropathy and microalbuminuria. The study was conducted to know the prevalence of diabetic retinopathy and its association with HbA1C, autonomic neuropathy and microalbuminuria in long standing diabetic patients of more than 5 years duration.

**Materials and methods:** A detailed hospital based cross sectional observational study was carried out at Department of Medicine, Dr. S. N. Medical College, Jodhpur Rajasthan (India) from April 2017 to June2018. 500 diabetes mellitus cases with more than 5 years of duration were chosen for the study and permission from institutional ethics committee was taken. Detailed history and medical examinations were conducted on the patients after obtaining the socio demographic information. Biochemical tests like HB1Ac, serum creatinine and urine albumin were conducted. Fundoscopy and autonomic nervous system monitoring was done. The data were statistically analysed using chi square test. P-value < 0.05 was considered as statistically significant.

**Results:** In the present study, diabetic retinopathy was observed in 45.8% cases. Out of these 55.9% had non-proliferative diabetic retinopathy and 44.1% had proliferative diabetic retinopathy. Autonomic nervous system test dysfunction was mild in 47% cases, moderate in 33.4% cases and severe in 19.6% cases. Occurrence of diabetic retinopathy was significantly associated with age, HbA1c level, urine albumin concentration, serum creatinine level and autonomic nervous system test dysfunction ($p<0.001$). The occurrence of ANST dysfunction severity with increasing HbA1c levels was also found to be statistically significant ($p<0.001$).

**Conclusion:** Prevalence of Diabetic retinopathy was found to be associated with the duration of diabetes, HbA1c level, ANST dysfunction and microalbuminuria. So, good glycaemic control could reduce the number of people who develop blindness due to diabetic retinopathy.

**Keywords:** Diabetes Mellitus, Diabetic Retinopathy, Diabetic Nephropathy, Autonomic Neuropathy, Hb1Ac, Microalbuminuria.

**Introduction**

Noncommunicable diseases (NCDs) kill 41 million people each year, equivalent to 71% of all deaths globally, of which Diabetes accounts for over 1.6 million. Diabetes mellitus (DM) is laso concerning because of the long term systemic complications that have substantial impact on the patient as well as society, as the disease typically affects individuals in their most productive years. NCDs disproportionately affect people in low- and middle-income countries not just because of their unhealthy lifestyle, but also delay in diagnosis and improper management which lead to predisposition for complications.

The leading cause of blindness between the ages of 20 to 74 in the United States is Diabetes mellitus and patients with diabetes are 25 times more likely to suffer with blindness than the ones without diabetes mellitus. Severe vision loss is primarily due to progressive diabetic retinopathy and clinically significant macular edema.[2]

Diabetic retinopathy is classified into two stages: non-proliferative and proliferative. Non-proliferative diabetic retinopathy (NPDR) usually appears late in the first decade or early in the second decade. The pathophysiologic mechanisms invoked in non-proliferative retinopathy include loss of retinal pericytes, increased retinal vascular permeability, alterations in retinal blood flow and abnormal retinal microvasculature; all can lead to retinal ischemia. The appearance of neovascularization in response to retinal hypoxemia is the hallmark of proliferative diabetic retinopathy (PDR). These newly formed vessels appear near the optic nerve and/or macula and rupture easily, leading to vitreous haemorrhage, fibrosis, and ultimately retinal detachment. Though all individuals with non-proliferative retinopathy develop proliferative retinopathy, the severity of non-proliferative disease correlates with greater chances of progression to proliferative retinopathy within 5 years. This suggests the importance of early detection and treatment of diabetic retinopathy in preventing blindness. Duration of diabetes mellitus and degree of glycemic control are the best predictors of the development of retinopathy.[3,4] The Diabetes Control and Complications Trial Research Group showed that, in type-1 diabetic patients, 10% reduction in the hemoglobin A1c (HbA1c) was associated with 43% and 45% diminution in improvement of diabetic retinopathy in the rigorous and traditional treatment group, respectively. Controlling diabetes and maintaining HbA1c level in the range of 6-7% can substantially reduce the progression of diabetic retinopathy.[5]

Diabetic nephropathy is the main cause of renal failure in diabetes. Microalbuminuria, the hallmark feature of diabetic nephropathy, is defined as albumin excretion of 30–299 mg in 24 hours. Without intervention, diabetic patients with microalbuminuria typically progress to proteinuria and overt diabetic nephropathy. This progression occurs in both type-1 and type-2 diabetes. Incidence of microalbuminuria in patients with type-1 diabetes was ~12% during a period of 7 years. In the United Kingdom Prospective Diabetes Study (UKPDS), the incidence of microalbuminuria

was 2% per year in patients with type-2 diabetes, and the 10–year prevalence after diagnosis was 25%. Renal disease, as evidenced by proteinuria and elevated blood urea nitrogen (BUN)/ creatinine levels, is an excellent predictor of retinopathy; both conditions are caused by diabetes mellitus–related microangiopathies, and the presence and severity of one reflects that of the other. Aggressive treatment of the nephropathy may slow progression of diabetic retinopathy and neovascular glaucoma.[6]

A serious and common complication of diabetes is Diabetic autonomic neuropathy (DAN). Major clinical manifestations of DAN include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, "brittle diabetes," and hypoglycemic autonomic failure. DAN may affect many organ systems throughout the body (e.g., gastrointestinal, genitourinary and cardiovascular). The present study was conducted to know the prevalence of diabetic retinopathy in western Rajasthan and its association with Hb1Ac, microalbuminuria and autonomic neuropathy in diabetes mellitus patients of more than 5 years duration.[7]

**Material And Methods**

A hospital based cross sectional descriptive study wascarried out in Department of Medicine, Dr. S.N. Medical College, Jodhpur (Rajasthan) from April2017 to June2018. Approval from institutional ethics committee was obtained for the study. An informed written consent of 500 Diabetes mellitus cases of more than 5 years duration was taken. Patients of either sex, more than 20 years of age and having Hb1Ac levels more than 7% were included in the study. Sociodemographic data like age and sex were noted and detailed history and clinical examination was done. Biochemical tests like Hb1Ac and serum creatinine were measured. Fundus examination was done by OIS Machine and autonomic nervous system test was done by Ewings machine. Data was collected and entered in Microsoft Excel 2010 Spreadsheets and statistically analysed using “chi square’ test. P-value < 0.05 was considered as statistically significant.

**Results**

Out of 500 diabetic cases included in the present study, 280 (56%) were males and 220 (44%) were females. Highest number of cases (33.0%) were in the age group 51-60 years followed by 61-70 years (29.4%) and 41-50 years (20.2%)(Table-1). 77.4% males and 72.6% females had diabetes mellitus between 5-10 years while 23.6% males and 27.4% females had diabetes more than 10 years (Figure-1).

Table-2 shows the results of fundoscopy. Diabetic retinopathy was seen in 45.8% (229/500) cases. Out of these 128 (55.9%) had non-proliferative diabetic retinopathy (NPDR) while 101 (44.1%) had proliferative diabetic retinopathy (PDR). Autonomic nervous system test dysfunction was mild in 47% cases, moderate in 33.4% cases and severe in 19.6% cases (Figure-2).

Non-proliferative diabetic retinopathy (NPDR) was seen in 28.57% of males and 21.82% of females while proliferative diabetic retinopathy (PDR) was found in 20.36% of males and 20% of females. The difference in prevalence of retinopathy amongst male and female subjects was however not found to be statistically significant ($p>0.05$). The occurrence of NPDR increased with age, affecting 37.5% cases of more than 70 years, 27.21% cases of 55-70 years, 19.73% cases of 40-54 years and 18.18% cases of less than 40 years. Similar trend was observed in occurrence of PDR.

Table-3 reveals that PDR was seen in 4.55% of DM patients aged <40 year, in 15.65% patients aged 40-54 years, 21.91% patients aged 55-70 years and 31.25% patients aged >70 years. This increase in NPDR and PDR with increasing age was found to be statistically significant (p<0.001) (Table-3).

The table-3 reveals that the occurrence of NPDR was seen in 18.41% DM patients with 7-8%, HbA1c levels, in 36.75% patients with HbA1c levels 8.1-10% and 28.07% patients with HbA1c levels >10%. The occurrence of PDR increased with HbA1c levels. The difference in NPDR and PDR occurrence with increasing HbA1c levels was found to be statistically significant (p<0.001). It was observed in the present study that the occurrence of NPDR and PDR was increased with increase in urine albumin concentration. The NPDR was seen in 3.28% of DM patients with nil urine albumin, in 28.19% patients with albumin 1+, 42.86% patients with albumin 2+ and 53.25% patients with albumin 3+ while PDR was seen in in 3.28% of DM patients with nil urine albumin, in 25.50% patients with albumin 1+, 32.97% patients with albumin 2+ and 35.06% patients with albumin 3+.The difference in NPDR and PDR occurrence with increasing urine albumin level was found to be statistically significant (p<0.001) (Table-3).

Patients with serum creatinine >1 mg/dl (36.82%) were more liable to have NPDR as compared to patients with serum creatinine ≤1 (13.64%). Similarly, PDR was more prevalent in patients with serum creatinine >1 mg/dl (25.97%) as compared to patients with serum creatinine ≤1 (14.05%). The difference in NPDR and PDR occurrence with increasing serum creatinine level was found to be statistically significant (p<0.001). The NPDR was seen in 48.98% DM patients with severe ANST dysfunction, in 35.33% patients with moderate ANST dysfunction and 8.94% patients with mild ANST dysfunction. Similarly, occurrence of PDR increased with severity of ANST dysfunction. The difference in NPDR and PDR with increasing severity of ANST dysfunction was found to be statistically significant (p<0.001) (Table-3).

The occurrence of severe ANST dysfunction was more in males (21.43%) as compared to females (17.27%). Similarly, moderate ANST dysfunction was also more common in males (33.93%) as compared to females (32.73%). The difference in occurrence of ANST dysfunction among male and female subjects was however not found to be statistically significant (p>0.05). The severe ANST dysfunction was seen in 12.32% patients with HbA1c levels 7-8%, in 27.67% patients with HbA1c levels 8.1-10 and 33.33% patients with HbA1c levels more than 10%. The occurrence of ANST dysfunction severity with increasing HbA1c levels was found to be statistically significant (p<0.001). (Table-4).

Table 1: Age Distribution of Study Subjects

| Age(in years) | No. of patients (n) | Percentage (%) |
|---|---|---|
| 20-30 | 3 | 0.60 |
| 31-40 | 36 | 7.20 |
| 41-50 | 101 | 20.20 |
| 51-60 | 165 | 33.00 |
| 61-70 | 147 | 29.40 |

| | | |
|---|---|---|
| ≥71 | 48 | 9.60 |
| Total | 500 | 100.00 |

Table 2: Fundus Photography Findings among Diabetic Patients

| Fundus Photography | No. of patients (n) | Percentage (%) |
|---|---|---|
| Normal | 271 | 54.20 |
| NPDR | 128 | 25.60 |
| PDR | 101 | 20.20 |
| Total | 500 | 100.00 |

Table 3: Association of various factors with Fundus Photography Findings

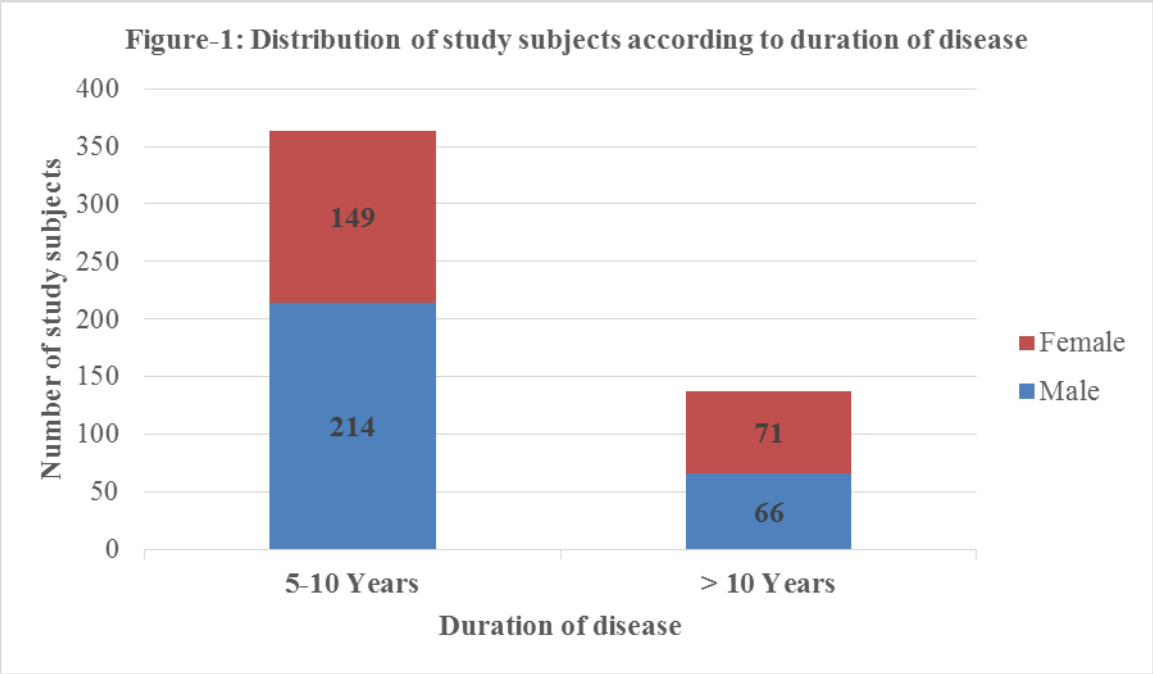
| Characteristic | Normal n (%) | NPDRn (%) | PDRn (%) | P-value* |
|---|---|---|---|---|
| Sex: | | | | |
| Male | 143 (51.07) | 80 (28.57) | 57 (20.36) | 0.187 |
| Female | 128 (58.18) | 48 (21.82) | 44 (20.00) | |
| Age (in years): | | | | |
| < 40 | 17 (77.27) | 4 (18.18) | 1 (4.55) | < 0.001 |
| 40-54 | 95 (64.63) | 29 (19.73) | 23 (15.65) | |
| 55-70 | 144 (50.88) | 77 (27.21) | 62 (21.91) | |
| > 70 | 15 (31.25) | 18 (37.50) | 15 (31.25) | |
| HbA1c: | | | | |
| 7-8 | 189 (68.23) | 51 (18.41) | 37 (13.36) | < 0.001 |
| 8.1-10 | 61 (36.75) | 61 (36.75) | 44 (26.51) | |
| > 10 | 21 (36.84) | 16 (28.07) | 20 (35.09) | |
| Urine Albumin: | | | | |
| Nil | 171 (93.44) | 6 (3.28) | 6 (3.28) | < 0.001 |
| 1+ | 69 (46.31) | 42 (28.19) | 38 (25.50) | |
| 2+ | 22 (24.18) | 39 (42.86) | 30 (32.97) | |
| 3+ | 9 (11.69) | 41 (53.25) | 27 (35.06) | |
| Serum Creatinine: | | | | |
| ≤1 | 175 (72.31) | 33 (13.64) | 34 (14.05) | < 0.001 |
| >1 | 96 (37.21) | 95 (36.82) | 67 (25.97) | |
| ANST Dysfunction: | | | | |
| Mild | 203 (86.38) | 21 (8.94) | 11 (4.68) | < 0.001 |
| Moderate | 68 (40.72) | 59 (35.33) | 40 (23.95) | |
| Severe | 0 (0.00) | 48 (48.98) | 50 (51.02) | |

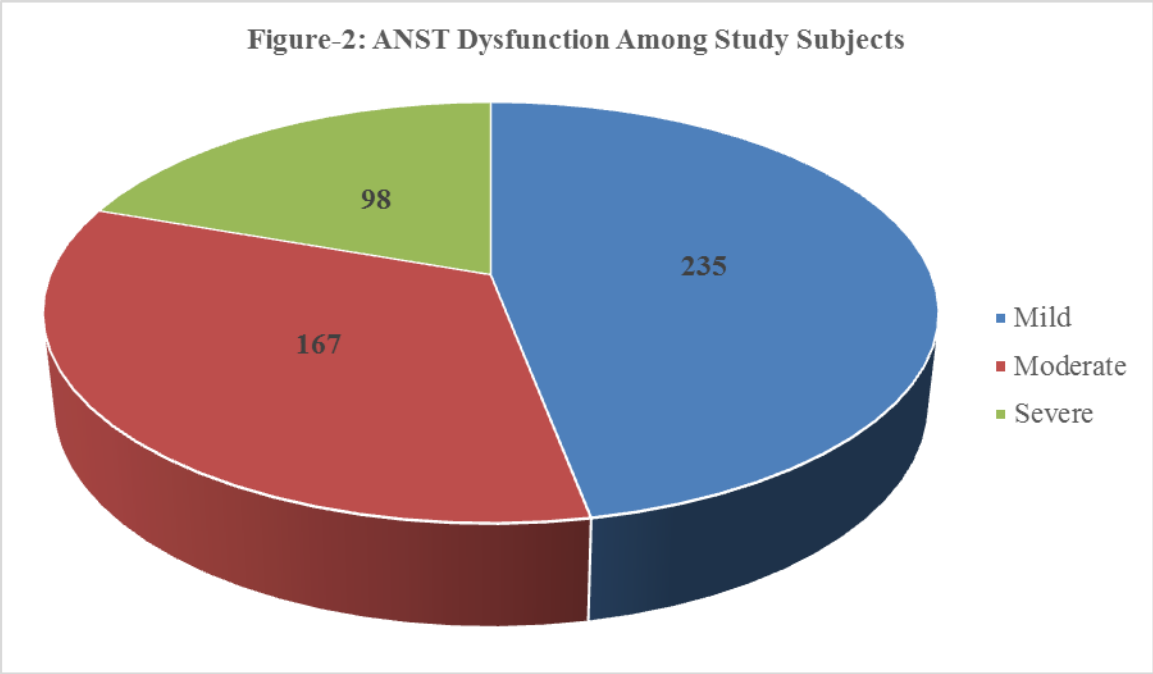
*Chi Square Test

Table 4: Association of Sex and HbA1c level with ANST dysfunction

| Characteristic | Mild n (%) | Moderate n (%) | Severe n (%) | P-value* |
|---|---|---|---|---|
| Sex: | | | | |
| Male | 125 (44.64) | 95 (33.93) | 60 (21.43) | 0.388 |
| Female | 110 (50.00) | 72 (32.73) | 38 (17.27) | |
| HbA1c: | | | | |
| 7-8 | 170 (59.86) | 79 (27.82) | 35 (12.32) | < 0.001 |
| 8.1-10 | 52 (32.70) | 63 (39.63) | 44 (27.67) | |
| > 10 | 13 (22.81) | 25 (43.86) | 19 (33.33) | |

*Chi Square Test





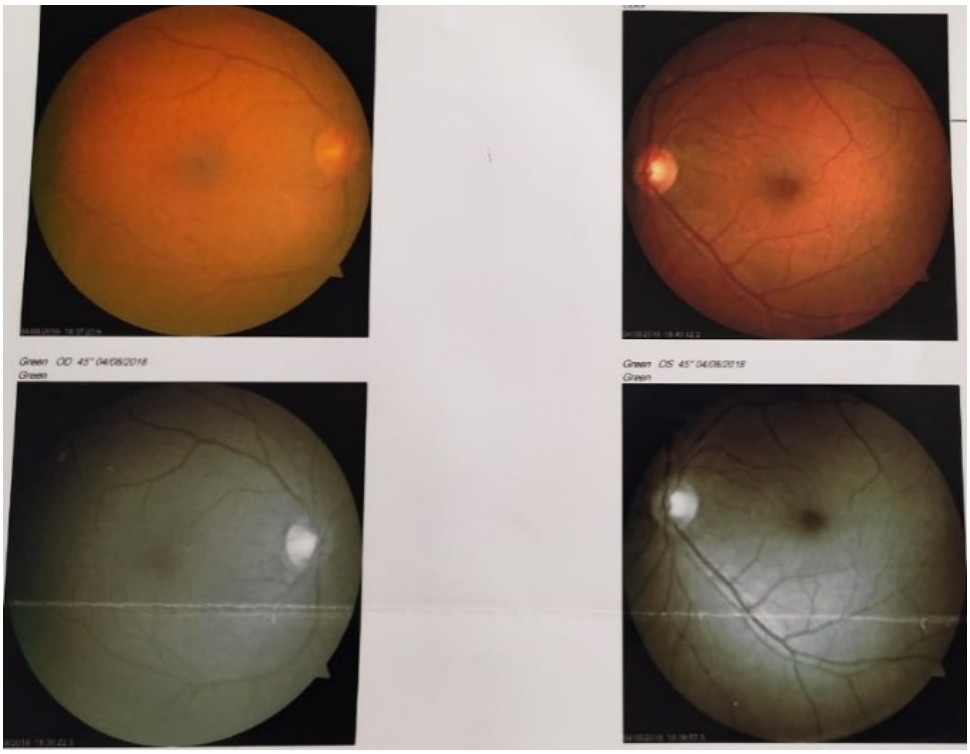



Fig.3: Bilateral hypertensive retinopathy and moderate non-proliferative retinopathy

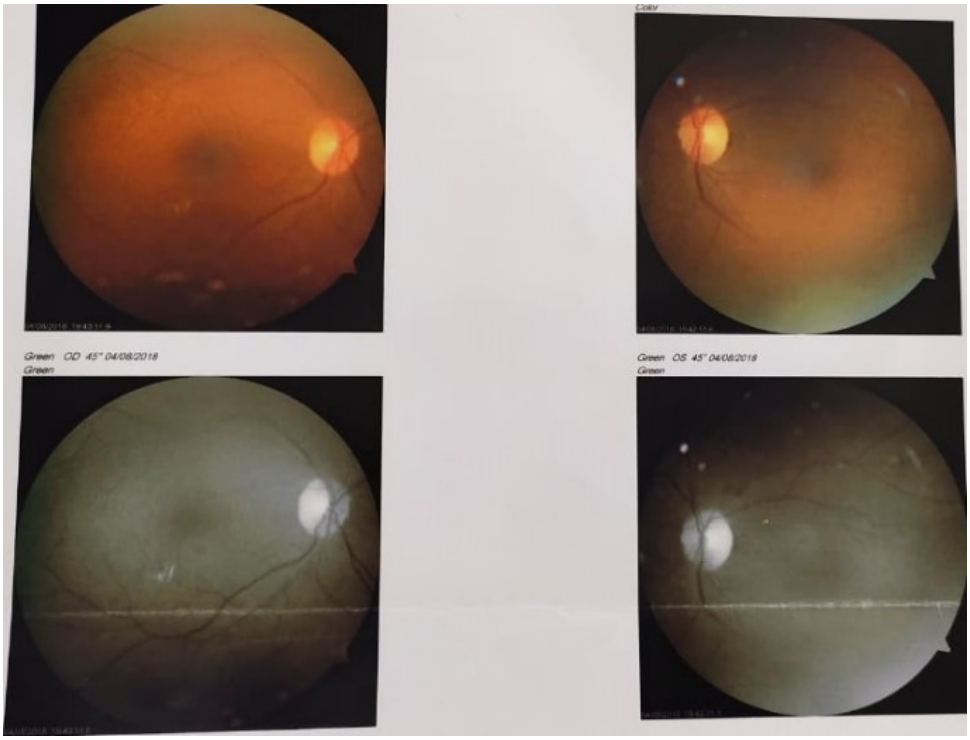



Fig.4: Bilateral mild diabetic retinopathy (Few microaneyrism+)

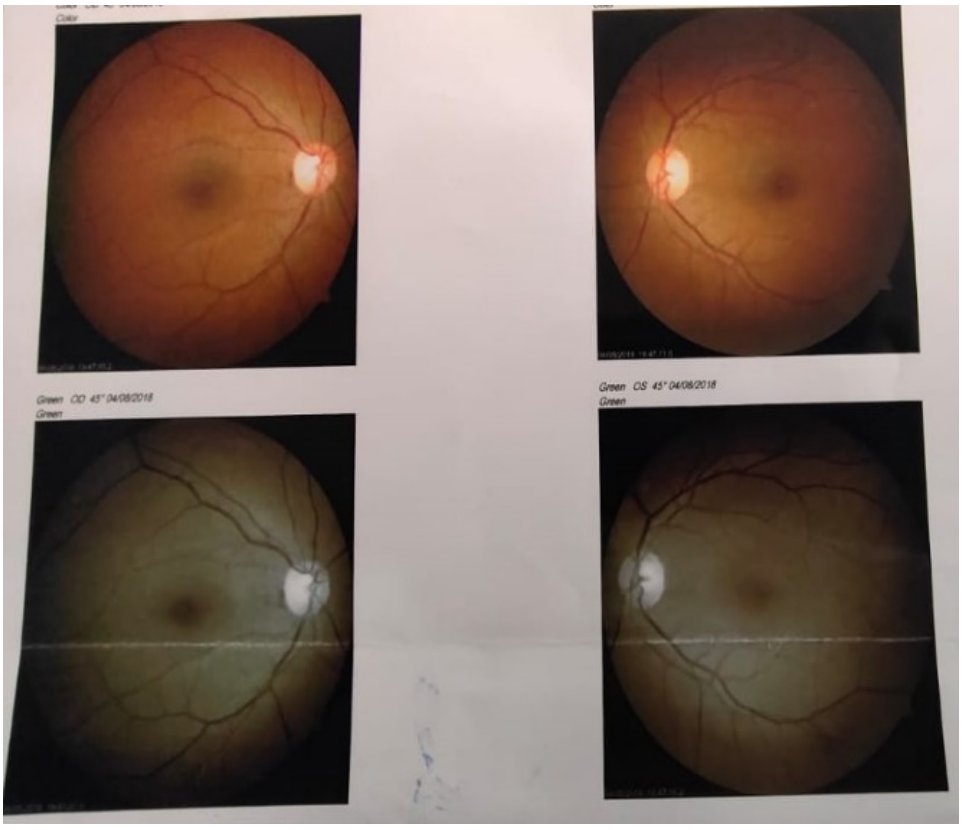



Fig.5: No diabetic retinopathy

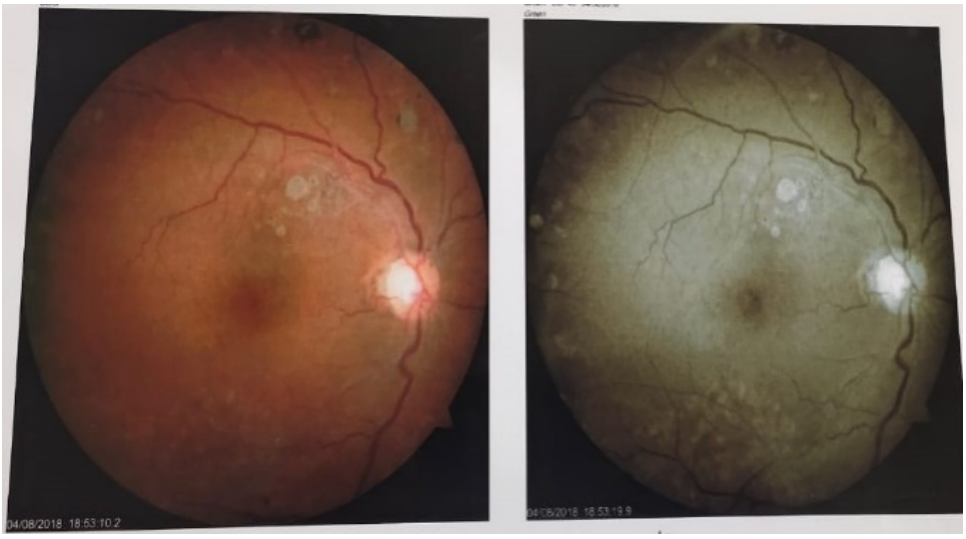


Fig.6: Lasered proliferative diabetic retinopathy with healed C&ME (Right Eye)

**Discussion**

Diabetic retinopathy is a specific microvascular complication of type-1 and type-2 diabetes. Duration of diabetes and hyperglycemia are two well known risk factors for the development of diabetic retinopathy. Kohner et al reported that up to a fifth of newly diagnosed type-2 diabetics have been found to have diabetic retinopathy.[8]

High glucose concentrations and chronic hyperglycemia leading to diabetic retinopathy is now a widely accepted hypothesis and a number of plausible biochemical pathways linking glucose metabolism directly to the development of diabetic retinopathy have been identified. The aldose reductase pathway, in which increased protein kinase C activity with increased vasodilatory prostaglandins production, increased non–enzymatic glycation and glucose induced auto–oxidative damage, occurs. Increased blood retinal barrier permeability and alterations in retinal blood flow may also be important in the pathogenesis. Thus, the biochemical, hemodynamic and hormonal mechanisms may interact together to produce the typical lesions of vascular occlusion, microaneurysms, hemorrhages, hard exudates and new vessels (neovascularization).[9]

In the present study, prevalence of diabetic retinopathy was 45.80%. The results were higher than that observed in Caucasians with type-2 DM from the United States (39%) and from South Africa (41%) and lower than that found in Caucasians from New Zealand (60%) and Caucasian from the South of Brazil (47%).[10] Internationally, the frequency of retinopathy has varied widely depending on the methodology and population sample.

The known duration of diabetes was one of the most important factors determining the presence of diabetic retinopathy. The results of present study indicated an association between prolonged duration of diabetes and increased prevalence of retinopathy with NPDR and PDR in the group who had diabetes for 5–10 years ($p<.001$) being significantly higher than the rest of the population. This is similar to the findings of Vinker et al.[11] and Romera et al.[12]

There was no significant association between gender and diabetic retinopathy. In the present study, 20.36% of males and 20% of females had PDR and NPDR was seen in 28.57% males and 21.82% females. These

finding was consistent with previous findings by Nakagami et al.[13] and Tapp et al.[14]

It was observed that HbA1c levels above 7.0% were significantly associated with increased prevalence of retinopathy. These findings were consistent with Sabanayagam et al who reported that increasing HbA1c categories had a higher prevalence of any retinopathy, mild retinopathy and moderate retinopathy. Many clinical trial results by the Diabetes Control and Complications Trial (DCCT)[15] and the epidemiological data from the Wisconsin Epidemiological Study of diabetic retinopathy had emphasized the strong relationship of glycemic control and development and progression of diabetic retinopathy. The American Diabetes Association (ADA) recommends that the mean HbA1c value should be kept below 7% to prevent diabetic micro and macrovascular complications.[16]

The present study clearly suggested that there was an association of severity of retinopathy with severity of autonomic neuropathy in type-2 DM. This confirms the finding of Smith et al.[17] and Krolewski et al.[18] PDR was seen in 51.02% patients with severe ANST dysfunction, in 23.95% patients with moderate ANST dysfunction and 4.68% patients with mild ANST dysfunction. Similarly, prevalence of NPDR increased with severity of ANST dysfunction. The PDR was seen in 3.28% patients with nil urine albumin, in 25.5% patients with albumin 1+, 32.97% patients with albumin 2+ and 35.06% patients with albumin 3+. Similarly, prevalence of NPDR was increased with urine albumin. The 2 years longitudinal study in Chile (36 and 64 subjects with microalbuminuria and normoalbuminuria, respectively) had shown that microalbuminuria from urine excretion in 24 hours was significantly associated with retinopathy[19]. The cross sectional study in Brazil[20] and Finland[21] showed that microalbuminuria is associated with proliferative diabetic retinopathy.

**Conclusion**

The present study showed strong association of diabetic retinopathy with duration of diabetes, HbA1c level, ANST dysfunction and microalbuminuria, but no association was found between gender and diabetic retinopathy. These findings contribute that decrease in HbA1c values or achieving ADA criteria can prevent or delay the onset/or progression of microvascular complications such as retinopathy. Regular screening for diabetic retinopathy and tighter glycaemic control could reduce the number of people who develop vision threating retinopathy.

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