# Predictors of severity of retinopathy among subjects with early onset type 2 diabetes mellitus

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## Abstract

**Purpose:** To explore the factors influencing the severity of diabetic retinopathy among early onset type 2 diabetes mellitus.

**Materials and Methods:** A descriptive cross sectional study was undertaken among subjects with early onset type 2 diabetes mellitus diagnosed with retinopathy. Demographic profiles like age, gender, duration of diabetes, co-morbidities and presence of macrovascular or microvascular complications were noted. Retina was evaluated using slit lamp biomicroscopy using 78D lens and Spectral Optical Coherence Tomography (OCT).

**Results:** The study group included 135 subjects. There were 78 NPDR and 57 PDR cases. Those with PDR had higher age, longer duration of diabetes, lower Hb values, higher HbA1C and higher urine micro-albumin. They had a higher triglyceride values and lower HDL values.

**Conclusion:** Higher age, longer duration, anemia, poor glycemic control and subclinical nephropathy were predictive of development of PDR among early onset type 2 DM subjects.

**Keywords:** Early onset diabetes mellitus, NPDR, HbA1C, PDR, Urine micro-albumin.

## Introduction

Retinopathy is the leading cause of blindness among persons with diabetes. Various factors have been identified as predictors of development of diabetic retinopathy and its progression. Most of the studies have been conducted among type 1 and late onset type 2 diabetes. This study intends to explore the factors influencing the severity of diabetic retinopathy among early onset (age of onset <40 years) Type 2 diabetes mellitus.

## Materials and Methods

A descriptive cross sectional study was conducted after obtaining permission from the Institutional Research & Ethics Committee. Sample size of 122 was calculated based on the formula 4pq/d2 where p=45, d=20% of p.

Subjects diagnosed with retinopathy among cases of early onset Type 2 diabetes mellitus (age of onset before 40 years) were selected. Juvenile diabetes mellitus, gestational diabetes mellitus, pancreatic diseases, other causes for endocrinopathies, steroid induced diabetes and genetic syndromes were excluded.

Demographic profiles like age, gender, socioeconomic status, duration of diabetes, co-morbidities like smoking, alcoholism, hypertension, obesity and hyperlipidemia were recorded. Presence of macrovascular (coronary artery disease, cerebrovascular events, peripheral vascular disease) and microvascular complications (neuropathy, nephropathy, and retinopathy) were noted. The subjects were grouped based on the presence or absence of at least one complication other than retinopathy). Retina was evaluated using slitlamp biomicroscopy using 78D lens and Spectral Optical Coherence Tomography (OCT). The status of the eye with worst retinopathy was considered for analysis.

Hb, fasting blood sugar (FBS), postprandial blood sugar (PPBS), glycosylated Hb level (HbA1C), blood urea, serum creatinine, urine micro-albumin and fasting lipid profile were recorded.

Based on ETDRS classification diabetic retinopathy was grouped as non proliferative diabetic retinopathy (NPDR) & proliferative diabetic retinopathy (PDR). NPDR was diagnosed by the presence of atleast one microaneurysm in the retina. Other findings seen in NPDR included hemorrhages, venous changes like dilatation, beading & looping, cotton wool spots and intraretinal microvascular anomalies. PDR was diagnosed by the presence of neovascularisation of retina. Other changes like preretinal hemorrhage, vitreous hemorrhage and fibrovascular changes also were observed in PDR. Statistical analysis was done using SPSS version 21. Independent T test was used to analyse the parameters. P value less than 0.05 was considered statistically significant.

## Results

The study group included 135 subjects. There were 78 cases with NPDR and 57 cases with PDR. Distribution of cases based on the demographic profile is given in Table 1. Those with PDR had higher age and longer duration of diabetes ($p<0.05$). Age of onset of the subjects with PDR was less than those with NPDR. However this was not statistically significant.

Distribution of cases based on risk factors and complications is given in Table 2. Microvascular complications were found to be more among those with

PDR. This observation was statistically significant (p 0.037).

Distribution of cases based on lab parameters is given in Table 3. Those with PDR had lower Hb values, higher HbA1C and higher urine micro-albumin. They had a higher triglyceride values and lower HDL values. These observations were statistically significant.

Those with NPDR were classified as mild, moderate, severe and very severe NPDR. PDR was grouped as early PDR, high risk PDR and advanced diabetic eye disease. The various parameters (Hb, HbA1C, urine micro-albumin, fasting lipid profile) were studied in relation to these subgroups. No statistically significant observations were made.

On multivariate regression analysis, duration of diabetes (beta error 0.7; p value 0.002), Hb gm% (beta error 3.4; p value 0.021) and HbA1C (beta error 3.1; p value 0.011) values were predictive on the development of proliferative diabetic retinopathy with overall fit of the model $R^2$ 14.4.

## Discussion

Severity of retinopathy in the form of proliferative diabetic retinopathy was associated with older age, earlier age of onset and longer duration of the disease. The mean age of subjects with PDR was higher than those with NPDR. Age of onset was lesser among those with PDR. This is reflective of the role of duration in the progression of the disease. There was no gender predilection. As the duration increased, the disease severity also increased. Tariq et al considers age group 41-50 years, male gender and positive family history of Diabetes Mellitus as predictors of severity of DR.[1] This is also in concordance with Song et al.[2] These researchers have suggested duration as an important predictor of retinopathy. This observation is significant even among late onset DM as reported by Henricson et al and Zhang et al.[3,4] Ahamed Razia et al observed that retinopathy was higher among patients who had developed diabetes at younger age (<45 years) compared with patients who developed diabetes beyond 45 years. Duration was a strong predictor for DR.[5] Leese et al found that duration of diabetes is a strong predictor for maculopathy and proliferative disease.[6]

Hypertension was not associated with severity of retinopathy. Hypertension has been closely associated with the onset, progression and severity of retinopathy among early onset diabetics. Various authors (Song et al, Jin P et al, Anan F et al, Son JW et al) have mentioned this association.[2,7-9] Forga L et al, Zhang et al, He BB et al and Hu M et al have observed similar relation between hypertension and retinopathy among older onset diabetics.[10,4,11,12] Lima et al observed that association between hypertension and DR varies in consistency and pattern.[13] Zheng et al concluded that isolated pressure measurements may not accurately represent continued effect of high pressure.[14] Ahamed et al noted that co existence of hypertension and nephropathy also appeared as significant predictor.[15] Leese et al noted that raised systolic blood pressure was a predictor of maculopathy. Even in absence of established hypertension, changes in homeostasis of blood pressure levels are considered as a co morbidity associated with the presence and severity of DR.

Microvascular complications were more among PDR. However associations between neuropathy and nephropathy with the severity of retinopathy could not be defined. Malagola R et al concluded that early onset type 2 diabetes mellitus had much higher risk of microvascular complications than matched control with Type I diabetes in spite of good glycemic control.[16] Ding j et al considers retinal vessel caliber as a potential tool to determine the incidence and progression of retinopathy in both Type I and Type 2 Diabetes mellitus. They concluded that among young type I diabetes narrow arteriolar caliber were consistently associated with PDR.[17]

It was observed that those with PDR were anemic. Association of anemia with diabetic retinopathy has been reported among elderly diabetics even without nephropathy. (Bahar A et al and Traveset et al).[18,19] They observed a prevalence of 26 to 56% among their study group. Bhaisakhiya et al noted that unrecognized anemia exists in diabetic subjects. The severity of anemia was greater in subjects with retinopathy.[20] Similar observation was made by Hosseni M S et al.[21]

HbA1C was more than normal among both NPDR and PDR. A statistically significant higher value was observed among PDR cases. Lima et al noted that hyperglycemia has a strong association with DR. Ahamed et al reported that glycemic control status of diabetic patient is a significant predictor of DR. According to Hoque et al, HbA1c categories >7.0% is an important risk factor for the development of retinopathy. Poor glycaemic control, advanced age, longer duration of diabetes and hypertension are other significant risk factors of diabetic retinopathy.[22] Yau J W et al also observed that longer diabetes duration and poorer glycemic and blood pressure control are strongly associated with DR.[23] Song et al found that higher proportion of early onset Type 2 diabetes mellitus subjects had suboptimal glycaemic control (HbA1C >7.5%) than late onset cohort.[24] Similar observations were made by Wilmot et al, Hussain S et al and Xu Y et al. [25-27] Niveditha H et al observed that those with raised HbA1C >8% developed PDR.[28] Blood urea and serum creatinine also showed a significant relation with severity of retinopathy. Leese et al suggests that raised HbA1C was important for developing proliferative retinopathy.

PDR was significantly associated with higher urine micro-albumin levels. Role of microalbuminuria as a marker of microvascular dysfunction and presence of DR has been reported. However further studies are needed to confirm this relationship with regard to the severity and type of diabetic retinopathy.[6,7,12,14]

The subjects also had high triglyceride and lower high density lipoprotein levels. Role of hyperlipedemia in prognosticating the severity of retinopathy is not yet defined. Mukherjee et al noted that apo B-100, total cholesterol, triglycerides and LDL cholesterol were the highest in severe NPDR cases.[29] Though hyperlipedemia and hypertriglyceridemia has been associated with onset of retinopathy and maculopathy its effect on the development of PDR is not extensively studied.[6,8,26,30] Ding J et al reports that dyslipidemia was a significant risk factor for development of diabetic macular edema in upto 7% cases.[17]

## Conclusion

Among young adults with early onset of diabetes mellitus, severity of retinopathy was associated with older age, earlier age of onset and longer duration of the disease. Microvascular complications were more among PDR. Anemia, poor glycemic control and elevated urine micro-albumin were predictive of PDR. Hypertriglyceredemia and lower levels of HDL cholesterol were observed among PDR cases.

**Table 1: Demographic profiles of subjects with NPDR and PDR**

| Significant Variables | | | Type of retinopathy | | | | | | P value |
|---|---|---|---|---|---|---|---|---|---|
| | | | NPDR (N2 78) | | | PDR (N2 57) | | | |
| Age (years) | | | 46.85 (SD 8.58) | | | 47.44 (SD 6.76) | | | 0.015 |
| Age of onset (years) | | | 33.13 (SD 5.85) | | | 31.54 (SD 6.02) | | | NS |
| Duration (years) | | | 14.22 (SD 7.25) | | | 15.55 (SD 6.31) | | | 0.001 |
| | | N1 | n | N1% | N2% | N | N1% | N2% | |
| Gender | Male | 84 | 47 | 55.95% | 60.25% | 37 | 44.04% | 64.91% | NS |
| | Female | 51 | 31 | 60.78% | 39.74% | 20 | 39.21% | 35.08% | NS |

NS – Not significant; N1% = (n/N1) x 100; N2% = (n/N2) x 100

**Table 2: Risk factors and complications in subjects with NPDR and PDR**

| Risk factors & complications | N1 | Type of Retinopathy | | | | | | P value |
|---|---|---|---|---|---|---|---|---|
| | | NPDR (N2=78) | | | PDR (N2=57) | | | |
| | | n | N1% | N2% | n | N1% | N2% | |
| Poor diabetic control | 129 | 75 | 58.13% | 96.15% | 54 | 41.86% | 94.73% | NS |
| Microvascular comp. | 67 | 37 | 55.22% | 47.43% | 30 | 44.77% | 52.63% | 0.037 |
| Neuropathy | 3 | 1 | 33.33% | 1.28% | 2 | 66.66% | 3.50% | NS |
| Nephropathy | 64 | 37 | 57.81% | 47.43% | 27 | 42.18% | 47.36% | NS |
| Macrovascular complications | 18 | 6 | 33.33% | 7.69% | 12 | 66.66% | 21.05% | NS |
| Cerebrovascular accidents | 4 | 0 | - | - | 4 | 100% | 7.01% | NS |
| Coronary artery disease | 12 | 6 | 50% | 7.69% | 6 | 50% | 10.52% | NS |
| Peripheral vascular disease | 2 | 0 | - | - | 2 | 100% | 3.50% | NS |
| Presence of at least one co morbidity | 94 | 55 | 58.51% | 70.51% | 39 | 41.48% | 68.42% | NS |
| a)Smoking | 19 | 9 | 47.36% | 11.53% | 10 | 52.63% | 17.54% | NS |
| b)Alcoholism | 4 | 3 | 75% | 3.84% | 1 | 25% | 1.75% | NS |
| c)Hypertension | 60 | 35 | 58.33% | 44.87% | 25 | 41.66% | 43.85% | NS |
| d)Hyperlipidemia | 49 | 26 | 53.06% | 33.33% | 23 | 46.93% | 40.35% | NS |
| Multiple co morbidities | 84 | 49 | 58.33% | 62.82% | 35 | 41.66% | 61.40% | NS |

NS – Not significant; N1% = (n/N1) x 100; N2% = (n/N2) x 100

**Table 3: Lab parameters among NPDR and PDR**

| Variables | Type of retinopathy | Mean | SD | P Value |
|---|---|---|---|---|
| Hb gm % | NPDR<br>PDR | 12<br>10.75 | 1.45<br>1.55 | 0.05 |
| ESR mm/hr | NPDR<br>PDR | 33.31<br>37.26 | 26.14<br>23.08 | NS |
| HbA1C % | NPDR<br>PDR | 8.41<br>9.82 | 1.31<br>1.649 | 0.04 |

| | | | | |
|---|---|---|---|---|
| B.urea mg % | NPDR<br>PDR | 39.29<br>36.25 | 24.71<br>17.59 | NS |
| S.creatinine mg % | NPDR<br>PDR | 1.65<br>1.65 | 1.236<br>1.142 | NS |
| Urine micro-albumin mg/dl | NPDR<br>PDR | 41.72<br>58.87 | 31.01<br>65.87 | 0.036 |
| Total cholesterol mg% | NPDR<br>PDR | 192.45<br>195.39 | 36.06<br>41.98 | NS |
| T G | NPDR<br>PDR | 133.59<br>146.82 | 51.30<br>68.20 | 0.033 |
| LDL | NPDR<br>PDR | 116.47<br>120.12 | 34.02<br>37.52 | NS |
| VLDL | NPDR<br>PDR | 29.10<br>30.23 | 9.64<br>10.79 | NS |
| HDL | NPDR<br>PDR | 45.99<br>44.40 | 6.22<br>8.19 | 0.021 |
| ratio | NPDR<br>PDR | 4.32<br>4.30 | 0.83<br>1.11 | NS |
| Na meq/l | NPDR<br>PDR | 139.62<br>140.65 | 4.81<br>4.13 | NS |
| K meq/l | NPDR<br>PDR | 4.45<br>4.42 | 0.71<br>0.56 | NS |

NS – Not significant

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