Original Article

# Diabetic Retinopathy Awareness and Associations with Multiple Comorbidities: Insights from DIAMOND Study

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## Abstract

**Background:** Diabetic retinopathy (DR) is leading cause of visual impairment in working-age adults. Macular edema can occur with or without other signs of retinopathy. **Methods:** This was a single-center, retrospective study conducted over 2 years in patients (>40 years of age) having type 2 diabetes mellitus (T2DM). Outcome measures were to analyze awareness and prevalence of DR and association of DR with identified risk factors. **Results:** Overall 6000 T2DM patients over 2 years were retrospectively evaluated. Almost 63% ($n$ = 3780) of patients were unaware that diabetes affects the retina. Almost 65% ($n$ = 3894) of patients were reported to have DR. Total 78.98% of males, and 69.50% of females had DR. There was a significant increase in the incidence of DR with age ($P < 0.00001$). Almost 60.80% ($n$ = 3653) of patients having DR were from working age group (40–70 years). Evidently, 42% ($n$ = 2520) of patients having DR had HbA1c > 9% ($P < 0.00001$). Overall 52.02% ($n$ = 1820) of smokers were reported of DR ($P < 0.00001$). With the increase in total cholesterol and triglycerides, there was a significant increase in DR incidence ($P < 0.00001$). A strong association was observed between hypertension and DR, with 42.6% ($n$ = 2556) of patients having coexistence of hypertension and DR ($P < 0.00001$). Patients having diabetic kidney disease (DKD) also reported DR. A high proportion of patients (49.11%, $n$ = 2947) had co-existence of cardiac morbidity and DR. Almost 47% ($n$ = 2845) of patients having DR were also reported anemia. Totally 43.85% ($n$ = 2631) of patients with microalbuminuria had two times more risk of developing proliferative DR ($P < 0.00001$). The statistical significance for the association of DR with risk factors, calculated by Pearson Chi-Square method of analysis was found statistically significant ($P < 0.00001$). **Conclusion:** The study reported the high prevalence and significantly high unawareness for DR in T2DM patients. All the risk factors are independently and significantly associated with DR ($P < 0.00001$).

**Keywords:** Diabetic retinopathy, India, nonproliferative diabetic retinopathy, proliferative diabetic retinopathy, type 2 diabetes mellitus

## Introduction

Diabetic retinopathy (DR) is a most important cause of impairment of vision among working-age individuals. Patients with diabetes mellitus (DM) have demonstrated defects in neurosensory function before the onset of vascular lesions.[1] The long duration of diabetes leads to microangiopathy changes which include protein synthesis in extracellular matrix and thickening of the capillary basement membrane.[2] In Indian type 2 DM (T2DM) patients of age ≥40 years, reported retinopathy prevalence was 21.7%.[3] Several published studies reported that in patients with diabetes the increase in cardiovascular (CV) risk was directly proportional to presence and severity of retinopathy.[4-9] Even at early stages of DR concurrence of microvascular and macrovascular abnormalities have been reported. The study also highlighted that all patients with significant macular edema should be screened for nephropathy.[10] The TREAT (Trial to reduce CV Events with Aranesp Therapy) study reported that retinopathy was noted in almost 47% of patients of T2DM with chronic kidney disease. Compared to the patients without retinopathy, longer duration of diabetes, more proteinuria and lower GFR were reported in retinopathy patients.[11] The objective of this study was to assess the awareness of DR and its association with multiple comorbidities. Risk factors studied for their associations with DR were, gender, age, smoking, glycemic control, diabetes duration, dyslipidemia, hypertension, microalbuminuria and diabetic kidney disease (DKD), anemia, and cardiac disease.

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## Methods

### Study design and data extraction

DIAMOND (DR Awareness and Associations with Multiple Comorbidities) study was a single-center; retrospective study conducted over 2 years. Data of patients with T2DM visiting a tertiary care hospital in Mumbai, India between 2013 and 2015 were collected and analyzed. Data recorded in electronic medical records were extracted and analyzed manually in January 2016. This data included patient demography, medical history, relevant current medical status, laboratory investigations, and medications prescribed.

### Patients

Inclusion criteria were patients with T2DM of age ≥40 years, whereas exclusion criteria were Type 1 diabetes (T1DM) and pregnancy.

### Outcome measures

The primary outcome measures of the study were to analyze awareness and prevalence of DR and to subsequently study the association of DR with identified risk factors including, gender, age, duration of diabetes, smoking status, glycated hemoglobin levels, treatment therapy for T2DM, lipid profile, hypertension, microalbuminuria, DKD, cardiac morbidity, and anemia. A validated questionnaire was used to assess awareness of DR. Dilated Fundus photos were taken on Carl Zeiss Fundus Camera. DR was graded by modified Airlie House Classification.

### Compliance with ethics guidelines

This study was conducted in accordance with the principles of the Declaration of Helsinki,[12] guidelines for good pharmacoepidemiology practice and local regulatory guidelines. Medical data of the patients who had given their prior consent was collected and analyzed in this study.

### Statistical analysis

The study results were statistically analyzed using "goodness of fit" or Pearson's Chi-square test for Independence. Discontinuous or categorical data are expressed as a percentage. *P* values were reported and interpreted at 5% level of significance.

## Results

### Baseline characteristics

Overall records and data of 6000 T2DM patients were analyzed. Baseline characteristics are given in Table 1.

### Awareness about diabetic retinopathy

Almost 63% ($n$ = 3780) of patients are unaware of the fact that diabetes affects the retina. Moreover, 68% ($n$ = 4080) of patients included in the study, were unaware if DR can be prevented or treated. Dilated fundus examination was not recommended to 73% ($n$ = 4380) of patients by their diabetes care provider. Majority of patients (92%, $n$ = 5520) had undergone first dilated fundus examination only when their vision was affected. When questioned for a reason for not seeking a retinal examination, 86% ($n$ = 5160) of patients reported "I can see everything" as the answer [Figure 1].

### Stages of retinopathy

Almost 65% ($n$ = 3894) of patients were reported to have DR, 28.58% ($n$ = 1715) of patients had only nonproliferative DR (NPDR), 19.51% ($n$ = 1171) of patients had proliferative DR (PDR). Totally 21.8% ($n$ = 1308) of patients had diabetic macular edema (DME). Among these, 13% ($n$ = 799) of patients were reported to have NPDR and DME, whereas 8.48% ($n$ = 509) of DME patients reported PDR + DME.

### Risk factors associated with diabetic retinopathy

#### *Gender and diabetic retinopathy*

Overall 79% ($n$ = 2763) of male and 69.50% ($n$ = 1739) of female patients had DR. Out of which, 53.80% ($n$ = 1882) and 25.18% ($n$ = 881) of male patients had NPDR and PDR, respectively. Similarly, 50.47% (1263) and 19% ($n$ = 476) of female patients had NPDR and PDR, respectively. DR was found to be associated significantly more with male patients compared to female patients ($P < 0.00001$) [Table 2].

#### *Age and diabetic retinopathy*

The incidences of DR increased with increasing age, 37.41% ($n$ = 485), 68.52% ($n$ = 1612), and 78.34% ($n$ = 1612) among 40–50 years, 51–60 years and 61–70 years age groups, respectively. NPDR showed higher prevalence than PDR in all the age groups except age group of 81–90 years. DR was associated found to be significant with the age of patients ($P < 0.00001$) [Table 2].

#### *Duration of type 2 diabetes mellitus and diabetic retinopathy*

The incidence of DR in patients with T2DM of at least 5 years was 65%. NPDR was noted higher than PDR in all the patients. A significant association was noted with DR and increase in diabetes duration ($P < 0.00001$) [Table 2].

#### *Smoking and diabetic retinopathy*

Overall 90% of smokers had DR. However, 59% of nonsmokers also reported DR. DR was found to be associated significantly with smoking ($P < 0.00001$) [Table 2].

#### *Glycemic control and diabetic retinopathy*

Incidence of DR was reported to be a minimum of 57.58% ($n$ = 364) for HbA1c range of 7%–7.9%, to a maximum of 68.63% ($n$ = 1394) for those with HbA1c >10%. In all the patients observed to have DR, NPDR was emerged as the type

**Table 1: Baseline characteristics**

| Total number of patients | 6000 |
|---|---|
| Age (years) | 65.2±25.1 |
| Sex, *n* (%) | |
| Male | 3498 (58.30) |
| Female | 2502 (41.70) |
| Duration of disease (years) | 11.9±6.9 |
| HbA1c (%) | 8.8±2.9 |

Data expressed as mean±SD. HbA1c: Glycated hemoglobin, SD: Standard deviation

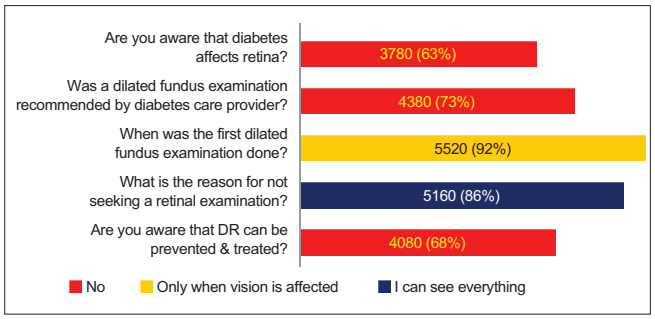


**Figure 1:** Awareness of diabetic retinopathy

with higher incidence rate as compared to PDR. There was a significant association between poor glycemic control and DR ($P < 0.00001$) [Table 2].

### *Treatment modality and diabetic retinopathy*

Almost 69% ($n = 2070$) of patients on oral hypoglycemic agents (OHA) had DR. Among these, 54.64% ($n = 1640$) of patients had NPDR. In patients on OHA and insulin treatment, 72.32% ($n = 2169$) of patients had DR, of which majority (40.31%, $n = 1209$) were diagnosed with PDR. DR was found to be associated significantly in patients with OHA and insulin treatment ($P < 0.00001$) [Table 2].

### *Lipid profile and diabetic retinopathy*

DR was reported in higher proportion of patients with total cholesterol >200 mg/dL as compared to those having total cholesterol <200 mg/dL (75.74% vs. 56.16%). Similarly, occurrence of DR was greater in patients with triglycerides >200 mg/dL as compared to those having levels of triglycerides <200 mg/dL (75.40% vs. 52.91%) NPDR was reported to have higher presence than PDR in all the DR groups, for both total cholesterol and triglycerides. DR was found to be associated significantly with disturbed lipid profile ($P < 0.00001$) [Table 2].

### *Hypertension and diabetic retinopathy*

Assessment for the presence of hypertension and DR revealed that 74.38% ($n = 2556$) of patients having hypertension also had DR. Hypertension and DR were found to have significant association ($P < 0.00001$) [Table 2].

### *Microalbuminuria and diabetic retinopathy*

Among patients who were reported to have microalbuminuria, significantly higher number of patients (85.8%, $n = 2631$) were detected with DR. DR was found to be associated significantly with microalbuminuria ($P < 0.00001$) [Table 2].

### *Diabetes kidney disease and diabetic retinopathy*

All the patients having DKD also reported to be detected with DR. More than half of DKD patients (56.61%, $n = 710$) had NPDR. Significant association between DR and DKD was observed ($P < 0.00001$) [Table 2].

### *Cardiac morbidity and diabetic retinopathy*

High proportion of patients (81.28%, $n = 2947$) included in the study had co-existence of cardiac morbidity and DR. The difference between the types of DR was not much in this population (NPDR - 43.22% vs. PDR - 38.06%). DR was found to be associated significantly with cardiac morbidity ($P < 0.00001$) [Table 2].

### *Anemia and diabetic retinopathy*

Among patients suffering from anemia, 84% ($n = 2845$) of patients also had DR, with higher occurrence rate for NPDR (52.80%, $n = 1789$). Anemia and DR were found to have significant association ($P < 0.00001$) [Table 2].

## Discussion

Diabetes leads to microvascular and macrovascular complications. Published evidence highlighted that DR is a major complication associated with T2DM. The present study provides data on prevalence and types of DR in individuals with T2DM assessed through validated questionnaire, and dilated fundus examination. We retrospectively studied the association of different risk factors with DR across 6000 type 2 diabetes patients. Most of our results complied with the conclusions of previously reported clinical studies.

Number of patients unaware of the fact that diabetes affects retina were very high in this study. Unawareness also existed among the patients regarding the fact whether DR can be prevented or treated. Majority of patients reported to have undergone first dilated fundus examination only when their vision was affected. Prevalence of retinopathy was found to be 65% in our study. This was found to be three times of the epidemiology (21.7%) reported in a recent Indian study.[3]

In this study, we observed men be more affected with DR as compared to women. LALES study highlighted 50% higher risk ($P = 0.006$) of DR in males versus Females.[13] Similarly, UK Prospective Diabetes Study (UKPDS) 50 study has reported that the relative risk for progression of DR was lower in women ($P = 0.0016$).[14]

The prevalence of DR was found to be higher in diabetic patients of ≥40 years ($P = 0.01$).[3] In the present study, incidence of DR increased with increase age. Only 37% of patients having any DR were below 50 years of age. Thus, age is an important risk factor for the development of DR.

Published studies reported that the duration of diabetes in patients with DR is almost double compared to patients without DR ($P < 0.0001$).[15,16] Wong *et al*. have reported that the odds ratio of DR increased by 1.07/year of the duration of disease.[17] In our study, diabetes for more than 5 years was associated with DR in more than half of patients ($P < 0.00001$).

In a 25-year follow-up study, mild NPDR was commonly reported among existing smokers compared to former smokers ($P = 0.038$) suggesting that its association with the development of DR.[18] In the present study, DR was noted significantly higher in smokers than nonsmokers.

Results from the Chennai urban, rural epidemiology study (CURES) eye study suggested that the prevalence of

**Table 2: Patients with any kind of diabetic retinopathy and associated risk factors**

| | No DR (%) | Any DR (%) | NPDR (%) | PDR (%) | *P** |
|---|---|---|---|---|---|
| Gender (*n*) | | | | | |
| Male (3498) | 735 (21) | 2763 (78.98) | 1882 (53.80) | 881 (25.18) | <0.00001 |
| Female (2502) | 763 (30.49) | 1739 (69.50) | 1263 (50.47) | 476 (19) | |
| Total (6000) | 1498 (24.96) | 4502 (75.03) | 3145 (52.41) | 1357 (22.61) | |
| Age group in years (*n*) | | | | | |
| 40-50 (1296) | 811 (62.57) | 485 (37.41) | 400 (30.86) | 85 (6.55) | <0.00001 |
| 51-60 (2352) | 740 (31.46) | 1612 (68.52) | 1207 (51.31) | 405 (17.21) | |
| 61-70 (1986) | 430 (21.65) | 1556 (78.34) | 799 (40.23) | 757 (38.11) | |
| 71-80 (294) | 125 (42.51) | 169 (57.47) | 100 (34.01) | 69 (23.46) | |
| 81-90 (72) | 0 | 72 (99.99) | 8 (11.11) | 64 (88.88) | |
| Duration of diabetes in years (*n*) | | | | | |
| <5 (632) | 250 (39.55) | 382 (60.43) | 308 (48.73) | 74 (11.70) | <0.00001 |
| 5-10 (956) | 330 (34.51) | 626 (65.47) | 525 (54.91) | 101 (10.56) | |
| 11-15 (1706) | 600 (35.16) | 1106 (64.82) | 681 (39.91) | 425 (24.91) | |
| >15 (2706) | 926 (34.22) | 1780 (65.77) | 1000 (36.95) | 780 (28.82) | |
| Smoking status (*n*) | | | | | |
| Smokers (2020) | 200 (9.90) | 1820 (90.09) | 1230 (60.89) | 590 (29.20) | <0.00001 |
| Nonsmokers (1478) | 600 (40.59) | 878 (59.39) | 531 (35.92) | 347 (23.47) | |
| HbA1c % (*n*) | | | | | |
| <6.9 (316) | 126 (39.87) | 190 (60.11) | 130 (41.13) | 60 (18.98) | <0.00001 |
| 7-7.9 (632) | 268 (42.40) | 364 (57.58) | 300 (47.46) | 64 (10.12) | |
| 8-8.9 (1195) | 375 (31.38) | 820 (68.61) | 470 (39.33) | 350 (29.28) | |
| 9-9.9 (1826) | 700 (38.33) | 1126 (61.66) | 710 (38.88) | 416 (22.78) | |
| >10 (2031) | 637 (31.36) | 1394 (68.63) | 904 (44.51) | 490 (24.12) | |
| Treatment (*n*) | | | | | |
| OHA (3001) | 931 (31.02) | 2070 (68.96) | 1640 (54.64) | 430 (14.32) | <0.00001 |
| Insulin + OHA (2999) | 830 (27.67) | 2169 (72.32) | 960 (32.01) | 1209 (40.31) | |
| Total cholesterol (*n*) | | | | | |
| <200 mg/dL (3327) | 1458 (43.82) | 1869 (56.16) | 1204 (36.18) | 665 (19.98) | <0.00001 |
| >200 mg/dL (2673) | 648 (24.24) | 2025 (75.74) | 1310 (49) | 715 (26.74) | |
| Triglycerides (*n*) | | | | | |
| <200 mg/dL (2804) | 1320 (47.07) | 1484 (52.91) | 1024 (36.51) | 460 (16.40) | <0.00001 |
| >200 mg/dL (3196) | 786 (24.59) | 2410 (75.40) | 1490 (46.62) | 920 (28.78) | |
| Hypertension (*n*) | | | | | |
| Yes (3436) | 880 (25.61) | 2556 (74.38) | 1650 (48.02) | 906 (26.36) | <0.00001 |
| No (2564) | 1220 (47.58) | 1344 (52.41) | 864 (33.69) | 480 (18.72) | |
| Microalbuminuria (*n*) | | | | | |
| Yes (3066) | 435 (14.18) | 2631 (85.80) | 1608 (52.44) | 1023 (33.36) | <0.00001 |
| No (2934) | 1671 (56.95) | 1263 (43.03) | 906 (30.87) | 357 (12.16) | |
| DKD (*n*) | | | | | |
| Yes (1254) | 0 | 1254 (99.99) | 710 (56.61) | 544 (43.38) | <0.00001 |
| No (4746) | 2106 (44.37) | 2640 (55.62) | 1640 (34.55) | 1000 (21.07) | |
| Cardiac morbidity (*n*) | | | | | |
| Yes (3625) | 678 (18.70) | 2947 (81.29) | 1567 (43.22) | 1380 (38.06) | <0.00001 |
| No (2375) | 1121 (47.20) | 1254 (52.80) | 876 (36.88) | 378 (15.91) | |
| Anemia (*n*) | | | | | |
| Yes (3388) | 543 (16.02) | 2845 (83.96) | 1789 (52.80) | 1056 (31.16) | <0.00001 |
| No (2612) | 1256 (48.08) | 1356 (51.90) | 771 (29.51) | 585 (22.39) | |

**P* for group comparison with Pearson Chi-square test of analysis. *n*: Number of patients, DR: Diabetic retinopathy, NPDR: Nonproliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy, OHA: Oral hypoglycemic agents, HbA1c: Glycated hemoglobin, DKD: Diabetic kidney disease

DR also increased significantly with increase in glycated hemoglobin levels.[19] Our results are in concordance with the previous reports of the strong and significant relation between the presence of DR and poor diabetes control. With the increase in the proportion of glycated hemoglobin, the number of patients with any DR increased progressively.

The UKPDS reported that degree of glycemic control was the most important component than the anti-diabetic medication

for prevention of retinopathy.[20] The study however reported, stronger and significant ($P < 0.00001$) association of DR with a combination of insulin and OHAs as compared to those on only OHAs.

In the present study, higher levels of total cholesterol and triglycerides were noted in the majority of patients having DR. Previously published studies have noted the relationship between retinal hard exudates with total cholesterol and low-density lipoprotein cholesterol in patients of DR.[21,22] Furthermore, CURES Eye study reported the association of total cholesterol, non-HDL cholesterol and serum triglycerides with DR.[23]

Aggressive BP control (144/82 mmHg) in patients with T2DM reported a decrease in the development of DR, loss of vision and requirement of laser photocoagulation versus less aggressive BP control (154/87 mmHg).[24] More than half of patients in this study presented with hypertension with DR. In addition, hypertensive patients were majorly detected with NPDR.

Reported evidence suggests that in patients with microalbuminuria and macroalbuminuria reported two times and six times higher risk of DR, respectively.[25] Furthermore, CURES study also reported that the patients with DR had significantly higher risk of nephropathy ($P < 0.0001$) compared to nonDR patients.[26] In our study, among patients reported with microalbuminuria, the majority had DR, with NPDR being higher prevalent. All the patients diagnosed with DKD had the presence of DR.

In our study, the significantly larger proportion of patients had co-existence of cardiac morbidity and DR, with NPDR being the major type. It has been noted that there is 1.7 times increased the risk of stroke, coronary artery disease, and heart failure in patients with T2DM with DR.[27] CAD was reported to be higher in DR group as per the data from CURES study.[28]

We observed the presence of DR in significantly high number of patients suffering from anemia in our study which is in accordance with a recently published study where there was a higher prevalence of anemia in individuals with DR was noted ($P < 0.001$).[29] Moreover, anemia has also been shown to aggravate hypoxia in the retina, thus leading to progression of DR.[30]

The main strengths were the availability of retinal photography screening data, categorization of DR in the patients' clinical records, use of a population-based database, large sample size, the inclusion of both gender, extensive age groups of patients were observed, and substantial analysis of relevant clinical data of the past 2 years. It is noteworthy that our results can be extremely relevant for clinical practice since the study was conducted in tertiary care hospital. Limitations of the study included the single center of study and noninclusion of T1DM patients.

## Conclusion

This retrospective study ($n = 6000$), conducted in a real-life scenario in Indian patients, reported the high prevalence and significantly high unawareness for DR in patients. Significant association of risk factors – male gender, higher age, longer diabetes duration, hyperglycemia, smoking history, insulin and OHA treatment, impaired lipid profile, high blood pressure, microalbuminuria, DKD, cardiac morbidity and anemia, with the association of DR in T2DM patients ($P < 0.00001$). The study has also categorized the observations according to the types of DR, including PDR and NPDR. NPDR was found to be the predominant type in this study.

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## Conflicts of interest

There are no conflicts of interest.

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