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Investigating Diabetic Retinopathy (DR) among individuals with Type 2 Diabetes Mellitus (T2DM)

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Abstract

Background: Diabetic retinopathy (DR) is a sight-threatening complication of type 2 diabetes mellitus (T2DM). Understanding its occurrence and associated factors is crucial for prevention and management. This study aimed to investigate DR in T2DM patients and identify relevant factors.

Methods: A 14-month hospital-based cross-sectional study was conducted at Bir Hospital, Kathmandu. Sixty T2DM patients were included, undergoing ocular examinations and fundus evaluations at Nepal Eye Hospital. DR severity was graded using the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria. HbA1C levels, fasting, and postprandial blood sugar were measured. Statistical analysis included chi-square test, t-test, and logistic regression.

Results: DR patients had a lower mean age (55.57±9.79 years) compared to non-DR patients (58.00±12.038 years, p=0.12). Age inversely correlated with severe DR (aOR=0.94, p=0.02). Longer diabetes duration increased DR likelihood (aOR=1.23, p=0.001) and severe DR risk (aOR=1.2, p<0.0001). Mean HbA1c was higher in DR patients (8.22±1.61%) compared to non-DR patients (7.48±1.59%, p=0.08), with marginal significance (aOR=1.44, p=0.09). Postprandial blood sugar was associated with DR (aOR=1.01, p=0.033), while fasting blood sugar was not significant. Hypertension was not associated with DR (p=0.89).

Conclusion: This study reveals higher prevalence and severity of DR with longer diabetes duration. Postprandial blood sugar showed significant association with DR, while fasting blood sugar did not. HbA1c's relationship with DR was marginally significant. Effective glycemic control and regular DR screening are crucial in T2DM patients.

Keywords: Diabetes mellitus; Diabetic retinopathy; Glycosylated hemoglobin; Fasting blood sugar; Postprandial blood sugar.

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1. Introduction

Diabetes mellitus is a set of metabolic disorders causing high blood sugar due to insufficient insulin secretion (type 1) or a combination of insulin resistance and inadequate secretion (type 2)[1, 2]. Type 2 diabetes mellitus (T2DM) constitutes about 85 to 95% of all diabetics in high income countries and accounts for an even higher percentage in low- and middle-income countries[3]. Globally, about 1 in 11 adults have diabetes mellitus (90% have type 2 diabetes mellitus (T2DM)), and Asia is the epicenter of this global T2DM epidemic[4].

There is a lack of reliable and representative data on the prevalence of type 2 diabetes in Nepal. Various small studies from different parts of the country carried out on the diverse populations have shown varying prevalence rates ranging from 6.3 to 8.5% [5]. In a nation-wide population study of urban Nepal, the prevalence of diabetes was 14.6% and 19% among the people 20 years and above and 40 years and above respectively[6].

The complications of diabetes mellitus have traditionally been divided into macrovascular complications (for example, cardiovascular disease (CVD)) and microvascular complications (for example, complications affecting the kidney, the retina and the nervous system) [7,8]. In a study across 28 countries in Asia, Africa, South America, and Europe, 50% of T2DM patients had microvascular complications and 27% had macrovascular complications[9].

Diabetic retinopathy is the most common microvascular complication of diabetes[10]. Diabetic retinopathy (DR) is a leading cause of visual disability and blindness in people with diabetes[11]. The risk of developing diabetic retinopathy or other microvascular complications of diabetes depends on both the duration and severity of hyperglycemia[3].

According to World Health Organization (WHO), DR is responsible for 4.8% of the 37 million cases of blindness throughout the world. The number of cases of DR is expected to grow from 126.6 million in 2010 to 191.0 million by 2030[12]. The worldwide prevalence of DR was found to be 34.6%. In a cross-sectional study done by Nepal Netra Jyoti Sangh, the prevalence of Non-Proliferative Diabetic Retinopathy (NPDR) was found to be 9.1% and Proliferative Diabetic Retinopathy (PDR) was found to be 0.5%[13]. A retrospective review done by Poudyal et. Al in a tertiary hospital of Nepal found that the prevalence of DR among patients with DM was 19.4%[14].

DR has been classified into two types based on level of micro vascular degeneration and related ischemic damage: Non-Proliferative Diabetic Retinopathy (NPDR) and Proliferative Diabetic Retinopathy (PDR). Proper detection and classification of patients with DR especially those with severe NPDR has great importance for prevention of visual loss through active intervention[15, 16].

Duration of diabetes and degree of hyperglycemia have consistently been identified as predictors of retinopathy[18]. Most patients with type I diabetes develop evidence of retinopathy within 20 years of diagnosis[19]. Retinopathy may begin to develop as early as 7 years before diagnosis of diabetes in patients with type 2 diabetes[10].

This study aims to enhance understanding of DR's epidemiology in relation to diabetes duration and glycemic control in Nepal, a developing nation. It can aid health policy makers in promoting health awareness, urging the inclusion of DR screening in smaller healthcare centers for prompt diagnosis, referral, and treatment.

2. Methodology

A hospital based cross-sectional study was conducted for 14 months from 2021/8/15 to 2022/8/15 at the Department of Internal Medicine, National Academy of Medical Sciences (NAMS), Bir Hospital, Kathmandu, Nepal, after obtaining approval from the ethical review committee of NAMS-Bir Hospital (Reference No.: 133712078179. Informed consent was taken from all participants.

The operational definition for selection of those patient is as follows: **Diabetes:** diagnostic criteria for DM are fasting plasma glucose ≥126 mg/dL (7.0 mmol/L), 2-hour plasma glucose ≥200mg/dL (≥ 11.1mmol/L) or glycated hemoglobinA_{1C} (HbA$_{1C}$) ≥ 6.5%.

2.1. Inclusion criteria

1. All diagnosed cases of Type 2 DM presenting to Internal Medicine OPD and admitted in the wards.

2.2. Exclusion criteria

1. Type I diabetic patients. 2. Patients with hazy ocular media. 3. Patients with history of laser photocoagulation. 4. Patients with shallow Anterior Chamber (AC). 5. Patients who have undergone intraocular surgeries like vitrectomy or retinal detachment surgery. 6. Patients not giving consent.

A total of 60 patients were included in the study. Data was collected and analyzed by using statistical software SPSS (Statistical Package for the Social Sciences) version 25. To implement different kinds of statistical tests, the characteristics of data was examined. Shapiro-Wilk test was carried to find the normality of distribution of data. All continuous data collected in the study were examined. Data was analyzed using chi-square test and independent t test. Binomial logistic regression and proportional ordinal logistic regression analysis was calculated among dependent variables and independent variables. p value <0.05 was taken as statistically significant.

3. Results

Among the 60 patients with T2DM, the age group ranged from 39 to 80 years. The maximum number of patients were in the age group 51-60 years. Overall mean age of the patients was 56.75±10.57 years. There was no significant difference in the age groups of patients with DR and no DR (p=0.968). Mean age in patients with DR and no-DR was 55.57±9.79 years and 58±12.038 respectively. No statistically significant difference was seen (p=0.127). There were 34 males (56.67%) and 26 females (43.33%). The ratio of male to female was 1.3. 19 males (54.28%) had DR compared to 16 females (61.53%). But there was no statistically significant difference (p=0.66

Table 1 Distribution of patients with DR in different age-group

Age groups	Diabetic Retinopathy		p-value
	Present	Absent	
31-40 years	3 (60%)	2(40%)	0.968
41-50 years	9(60%)	6(40%)	
51-60 years	12(63.15)%	7(36.85%)	
61-70 years	6(54.54%)	5(45.45%)	
71-80 years	5(50%)	5 (50%)	

The overall prevalence of Diabetic retinopathy in diabetics was 58% of which PDR accounted for majority (23%) whereas moderate NPDR was least prevalent (10%).
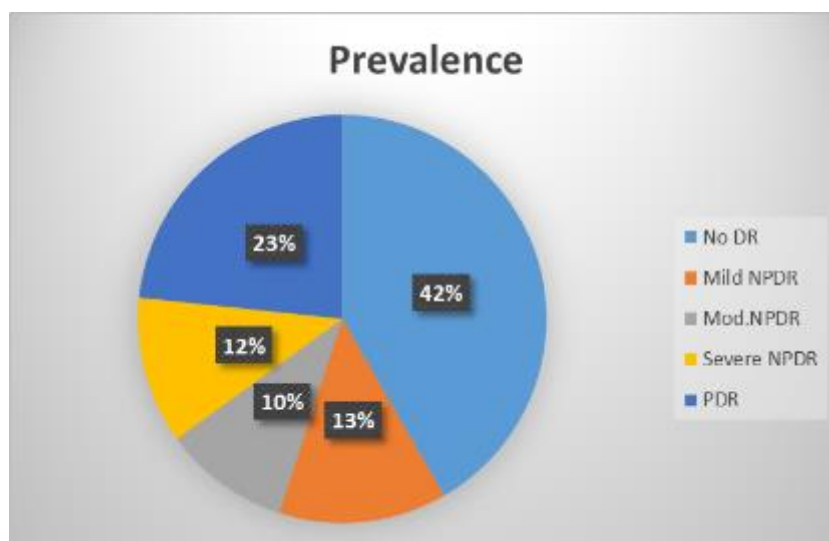

Figure 1 Prevalence of diabetic retinopathy

Proportionately high prevalence of PDR was seen in group of diabetes duration 20-30 years (66.7%) and 10-20 years (31.8%). Duration group of 0-10 years and 10-20 years had all form of NPDR with proportionately higher prevalence in 10-20 years.
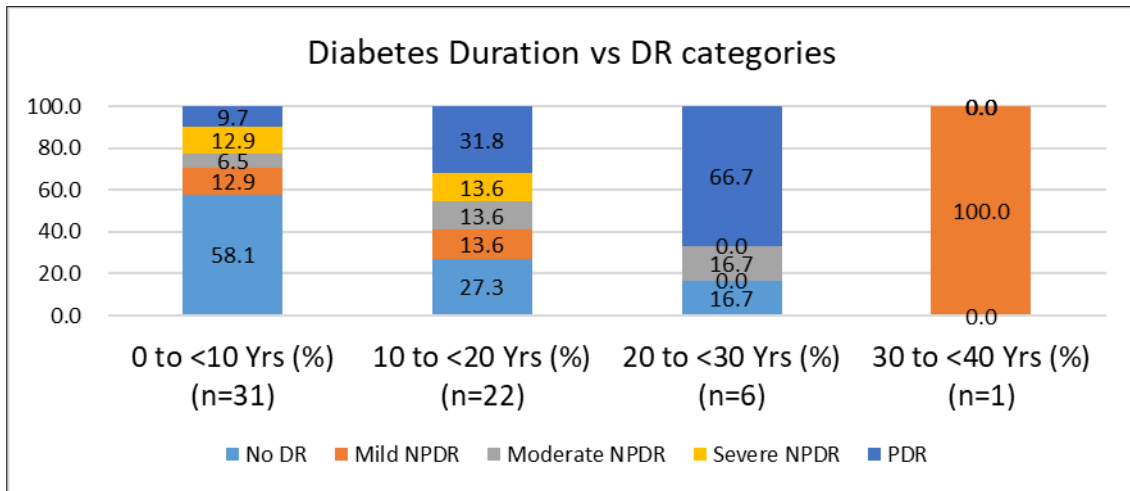

Figure 2 Distribution of different diabetic retinopathies in patients having diabetes for different duration

The majority had either good (38.33%) or fair (33.33%) glycemic control. Nearly half of these group had no Diabetic retinopathy. Proportionately larger population with poor glycemic control had either non-proliferative (53%) or proliferative (29.4%) diabetic retinopathy.
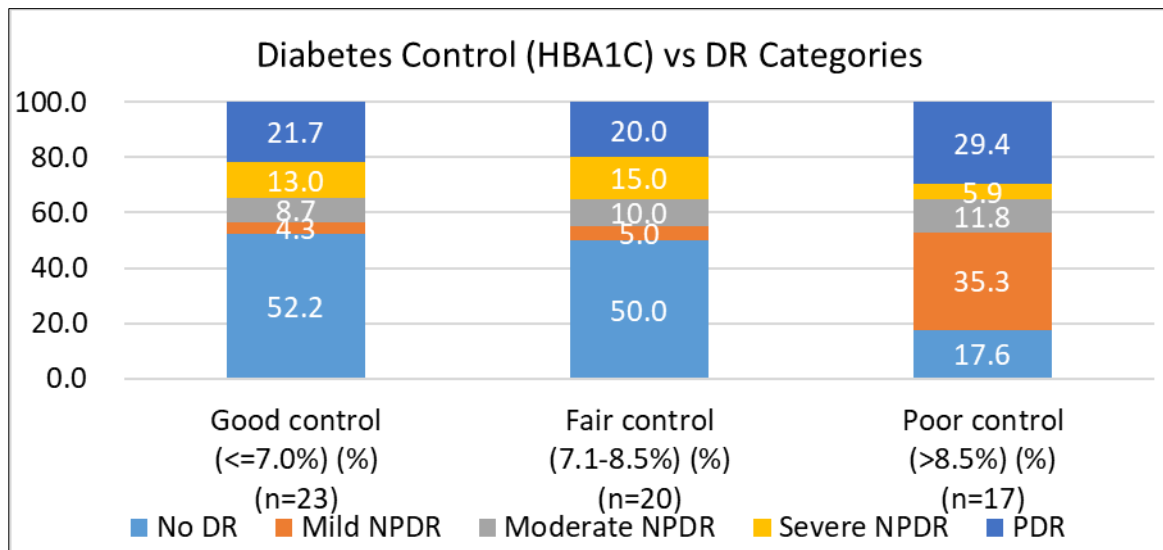

Figure 3 Distribution of different diabetic retinopathies in patients of different glycemic control categories

The distribution of different diabetic retinopathy status was very similar in in patients with or without hypertension. The proportion patients with no DR, mild NPDR, moderate NPDR, severe NPDR and proliferative DR in hypertension group were 39.5%, 13.2%, 13.2%, 10.5%, and 23.7%. Similarly, the proportions were 25.5%, 13.6%, 4.5%, 13.6% and 22.7% respectively in patients without hypertension. Chi squared test did not reveal any difference (p=0.89).

Table 2 Distribution of different diabetic retinopathies in patients with or without hypertension

HTN		No DR	Mild NPDR	Moderate NPDR	Severe NPDR	PDR	Total	Chi. Sq. P-vale
HTN No	n	15	5	5	4	9	38	0.89
	%	39.5	13.2	13.2	10.5	23.7	100	
HTN Yes	n	10	3	1	3	5	22	
	%	45.5	13.6	4.5	13.6	22.7	100	

The effect of different variables on the occurrence of diabetic retinopathy (any type, any severity) was measured using binomial logistic regression. One unit (one year) increase in the duration of diabetes increased the chance of getting diabetic retinopathy by 1.23 times (aOR = 1.23, p=0.001). There was no statistical significant relationship between HBA1C and diabetic retinopathy (aOR = 1.44, p=0.09). Though each of HbA1c, FBS and PPBS measure the diabetic status, additional binomial logistic regression was carried by replacing HbA1c with either FBS or PPBS. While FBS showed no relation with DR (p=0.37), PPBS showed significant association with DR and every one unit increase in PPBS increased the odds by 1.01 times (aOR=1.01, p=0.033).

Table 3 Logistic regression for outcome of diabetic retinopathy in general against various study dependent variables

Description	adjusted Odds Ratio (aOR)	95% Confidence Interval (CI), LL (Lower Limit)	95% CI, Upper Limit (UL)	p value
(Intercept)	0.29	0.001	57.703	0.646039
AGE	0.95	0.885	1.018	0.144173
SEX: Female	1.26	0.330	4.809	0.736285
HTN: Yes	0.43	0.104	1.813	0.252342
DURATION	1.23	1.091	1.395	0.000824
HBA1C	1.44	0.944	2.211	0.090184

4. Discussion

Diabetic Retinopathy (DR) is a retinal vascular disorder that is a leading cause of preventable blindness and occurs as a long-term complication of DM[11]. The modifiable and non-modifiable risk factors of DR include blood glucose level, BP, duration of diabetes, gender and age[20].

Review of existing literature revealed that, so far, multiple studies have been conducted to find out the association between diabetic retinopathy and duration of diabetes or glycemic status among Nepalese diabetic population. However very few studies are conducted in tertiary level multispecialty hospital. Also there are varying prevalence of diabetic retinopathy among diabetics in different studies. Thus, this study was conducted with the aim to find out if there is any association between DR and duration of diabetes or glycemic status of patients presenting to medical OPD either with ocular or other complains and also if any risk factors have any effect on this correlation.

60 patients with type II DM were included in this study as per the inclusion criteria laid down in the methodology. The age group ranged from 39 to 80 years. The maximum number of patients were in the age group 51-60 years. Overall mean age of the patients was 56.75±10.57 years. There was no significant difference in age groups (p=0.968). Mean age in patients with DR and no-DR was 55.57±9.79 years and 58±12.038, respectively. No statistically significant difference was seen (p=0.127). There were 34 males (56.67%) and 26 females (43.33%). The ratio of male to female was 1.3. Though proportionately, slightly more females (61.53%) than males (54.28%) have diabetic retinopathy, there was no statistically significant difference (p=0.66). The study done by Long M et al.[21] reported a mean age of 61.24±0.46 with no significant association (p=0.108). But male gender was associated with increased severity of retinopathy (odds ratio (OR): 1.602, p = 0.001). Cetin EN et al. reported[22] that the groups were well-balanced in terms of age and gender

(p =0.071 and p=0.265 respectively). Another study showed that the mean age was 61.86±8.03 with p-value of 0.0372 which shows that NPDR subject were older than PDR subject. There was no significant difference in gender (P=0.605)[23].

Of total of 60 patients enrolled in this study, overall prevalence of Diabetic retinopathy in diabetics is 58% of which PDR accounts for majority (23%) whereas moderate NPDR is the least in prevalence (10%). Zhang et.al [24]observed that the estimated prevalence of diabetic retinopathy and vision-threatening diabetic retinopathy was 28.5% (95% confidence interval [CI], 24.9%-32.5%) and 4.4% (95% CI, 3.5%-5.7%) among US adults with diabetes, respectively. Shrestha MK et al [25] in a hospital based study in Nepal found that the prevalence of Diabetic Retinopathy was 44.7% (166) with non-proliferative Diabetic Retinopathy presented 85.5% (142) and 14.5% (24) were proliferative Diabetic Retinopathy.

In this study, there was a general trend of increasing prevalence of DR as the duration of diabetes increased. Majority of patient (58.7%) in diabetes duration of 0-10 years had no diabetic retinopathy whereas no patient were without diabetic retinopathy in 30-40 years group. Mean was also calculated for duration of diabetes in patients with and without DR which was 12.43 +-7.29 years and 5.38 +- 5.78 years respectively. The difference was very significant (p<0.00).The duration of diabetes was correlated with the occurrence of severe forms of DR which was statistically significant. Every one unit (one year) increase in duration of diabetes increased the chance of getting severe form of diabetic retinopathy by 1.2 times (aOR = 1.2 times, p<0.0001).

Shakya K et al.[26] also reported that the duration of diabetes was significantly longer in the DR group compared to no DR group (p=0.006). 60% of diabetics of 10-12 years duration had DR, whereas 7.7% - 12.9% of diabetics of 0 to 2 year-duration had DR. Varma R et al.(63) reported that on average, each year of longer duration of diabetes was associated with an 8% higher risk of having any DR. Ilechie A et al.[27] concluded that prevalence of retinopathy significantly increased with increase in duration of diabetes (<5 years, 1.1%; 6-10 years, 3.3%; 11 years and above, 100% [$p<0.001$]). Various studies also reported that patients with DR had longer duration of diabetes.

Glycated hemoglobin (HbA1c) is a common marker used to monitor glycemic control. Elevated HbA1c suggests a poorly controlled diabetes which is one of the risk factors for DR. In this study, out of 17 patients with poor HbA1c level, 3 (17.6%) had no DR, 6 (35.3%) had mild NPDR,2 (11.8%) had moderate NPDR,1 (5.9%) had severe NPDR and 5(29.4%) had PDR. Mean HbA1c level in DR group (8.22±1.61%) was higher than in no DR group (7.48±21.59%). There was no statistically significant difference seen (p=0.082).

But when all the other variables used in the regression were kept constant, There was no statistically significant relations hip between HBA1C and diabetic retinopathy (aOR = 1.44, p=0.09).

But various studies have concluded HbA1c to be an independent risk factor for DR. A higher HbA1c has shown association with both increased incidence and progression of DR.(29,70–72) The LALES study reported that with every 1% increase in HbA1c, there is a 22% increase in prevalence of DR. In a study done in Nepal by Shakya K et al.[28], the mean HbA1c level was 7.0±1.2. The HbA1c value was significantly higher in DR group than in no DR group (p=0.004).

The fasting blood glucose level, which is measured after a fast of 8 hours, is the most commonly used indication of overall glucose homeostasis, largely because disturbing events such as food intake are avoided. The metabolic response to a carbohydrate challenge is conveniently assessed by a postprandial glucose level drawn 2 hours after a meal or a glucose load.

In this study it is observed that mean fasting blood sugar was least (124.08mg/dl) in patient with good glycemic control (HbA1C<=7%) and highest (194.33mg/dl) in patients with poor glycemic control (HbA1C>=8.5%).There is significant relation (p value <0.001) between mean fasting blood sugar and glycemic control of the patients.

Similarly, the patients with good glycemic control had the least mean postprandial blood sugar(165.38mg/dl) whereas those with poor glycemic control had the highest mean postprandial blood sugar(280.80mg/dl).There is also significant relationship (p value<0.001) between mean postprandial blood sugar and glycemic control. A study done by Shrestha L et.al[29] showed that both postprandial blood glucose and fasting blood glucose significantly correlated with HbA1c. Postprandial blood glucose showed better correlation to HbA1c than fasting blood glucose (r = 0.630, P <.001 vs. r=0.452,p=0.05). Kikuchi et.al [30] found that there existed a progressive shift in the contribution of fasting and postprandial hyperglycemia to the overall hyperglycemic status with progression from moderate to severe diabetes mellitus.

Dr. Sweta NK[31] concluded that as there was significant correlation between HbA1c & FBS, PPBS & RBS ('p'value- : <0.010), in resource poor settings & in conditions with limitations for using HbA1c, FBS & PPBS can be used to monitor

the glycemic control.Eventhough,HbA1c remains the gold standard in assessment of glycemic control with availability of standardized methods.

This study also found that while FBS showed no relation with DR (p=0.37), PPBS showed significant association with DR and every one unit increase in PPBS increased the odds by 1.01times (aOR=1.01, p=0.033). However effect of FBS or PPBS on gradual increase in severity of diabetic retinopathy from no retinopathy to mild, moderate, severe NPDR and proliferative DR revealed no change in association. (p=0.76 for FBS and 0.2 for PPBS)

Shiraiwa et.al observed that postprandial plasma glucose levels (odds ratio 1.008, P = 0.016) correlated with the progression of diabetic retinopathy. Liu Y et.al found that higher postprandial blood glucose (PBG), HbA1c, triglyceride and low-density lipoprotein were independent risk factors for DR only, and higher FBG was a risk factor for sight threatening DR only. Wong TY et.al[32] concluded that there was no evidence of a clear and consistent glycaemic threshold for the presence or incidence of retinopathy across different populations and he current FBS cutoff of 7.0 mmol/L used to diagnose diabetes did not accurately identify people with and without retinopathy.

In this study,22 patients had HTN of which only 12 (54.54%) had DR. Similarly, out of 38 patients with no HTN, 23(60.52%) had DR. HTN was not statistically significant (p=0.89). Agroiya P et al.[33] reported a statistically significant positive correlation of severity of DR with both systolic BP (p=0.005) and diastolic BP (p=0.001). The Hoorn study suggested that hypertensive patients had twice the risk of developing retinopathy after 10 years than diabetic patients with normal BP[34]. The Los Angeles Latino Eye Study (LALES) study showed an odd ratio of 1.26 (P=0.002) for every 20 mm Hg increase in BP[35]. Funatsu H et al. [36] showed an association between progression of NPDR and systolic BP (OR 1.72; 95% CI 1.14-2.91). But there was no significant association between progression of NPDR and diastolic BP. Various studies have reported HTN to consistently have a positive association with DR. Unlike some of the above studies, we did not the compare the systolic and diastolic BP values with DR, as most of the patients were taking anti- hypertensive medication and their BP were within normal level at the time of presentation.

5. Conclusion

Based on this study, we concluded that there is significant association between duration of diabetes and DR and also its severity in patients with T2DM. Similarly PPBS was also significantly associated with occurrence of DR while HbA1c is only marginally significantly related. On the other hand, Increasing Age is shown to be significantly related to severity of DR. Thus, Effective glycemic control and regular DR screening are crucial in T2DM patients.

However, we would also like to recommend that several such large scale studies (also including Type 1 DM patients) should be conducted; follow up should be done to assess the progression of severity of DR and change in glycemic status; and clinical features of target organ damage like nephropathy, neuropathy, ischemic heart disease and cerebrovascular disease should be taken into considerations.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

Prior conducting the study, Ethical Approval was obtained from the ethical review committee of National Academy of Medical Sciences (NAMS)-Bir Hospital (Reference No.: 133712078179).

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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