Diabetic retinopathy in patients with newly diagnosed type 2 diabetes mellitus

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Abstract

Introduction: Diabetic retinopathy (DR) is the leading cause of visual impairment worldwide including Nepal and studies from populations have shown that up to 10% of diabetic patients have vision-threatening DR, with up to 5% requiring treatment at this initial visit. Within this context, this study aims to evaluate the presence of DR in newly diagnosed diabetic patients, presenting in the outpatient department of ophthalmology, at Patan Academy of Health Sciences.

Method: It is a retrospective cross-sectional study carried out in referred cases of newly diagnosed type 2 Diabetes Mellitus (DM) from January 2021 to December 2022. Information regarding age, gender, Body Mass Index (BMI), blood pressure (BP), Triglyceride (TG), proteinuria, and findings of fundus evaluation were extracted from the record maintained in the Department of Ophthalmology.

Result: Out of 102 patients with mean age of 49.1±13.6 y, 14(13.73%) had DR, 11(10.8%) had mild Non-proliferative Diabetic Retinopathy (NPDR) and three (2.9%) had moderate NPDR. There was female predominance 56(54.9%), 50(49%) patients were overweight or obese (BMI≥25 kg/m2), 15(14.7%) patients had proteinuria and 28(27.5%) had fasting hypertriglyceridemia and additional ocular anomaly was identified in 33(32.4%) patients.

Conclusion: Diabetic retinopathy is already present in significant proportion of newly diagnosed type 2 DM patients. Routine screening for DR at the time of diagnosis can improve ocular outcomes in newly diagnosed diabetics with targeted early treatment. Future research should evaluate this in wider population to generate guidelines for need of mandatory eye evaluation at diagnosis.

Keywords: blindness, diabetes mellitus, diabetic retinopathy, Nepal
Introduction

Diabetic retinopathy (DR) is the leading cause of visual impairment among working aged individuals in both western worlds as well as in Nepal.\textsuperscript{1-4} Detailed understanding of the prevalence of Diabetes Mellitus (DM), as well as the association of DR with other detectable conditions allows for improved awareness, screening and treatment, and subsequently lower incidence and severity of vision loss.\textsuperscript{1-4} Previous population-based screening studies from Nepal have shown a higher percentage prevalence of DR than India.\textsuperscript{4} Different community based screening for DR found a prevalence of 19.3%,\textsuperscript{5} and a subsequent community-based study in two different metropolitan cities of Nepal reported a slightly lower DR prevalence of approximately 12%.\textsuperscript{6}

In addition, studies from populations in Southeast Asia and Oceania have shown that up to 10% of diabetic patients have vision threatening DR at initial presentation, with up to 5% requiring treatment at this initial visit.\textsuperscript{7,8} The studies demonstrate that Glycosylated Hemoglobin (HbA1c), Body Mass Index (BMI), duration of diabetes, microalbuminuria are known for risk factors of diabetic retinopathy and its progression.\textsuperscript{9} This highlights the importance of diagnosing severity of DR at presentation and its need for treatment in addition to determining DR prevalence. Data on prevalence and severity of DR at the time of diagnosis of type 2 DM in Nepal is scarce.

Within this context, this study aims to evaluate the presence of DR in newly diagnosed diabetic patients and associated risk factors presenting in the outpatient Department of Ophthalmology, at Patan Academy of Health Sciences (PAHS).

Method

This was a retrospective study conducted at PAHS. The study population included patients attending to ophthalmology department from January 2021 to December 2022 after being referred from medicine outpatient department with new diagnosis of type 2 DM. Data was retrieved from the hospital records present in ophthalmology department. Hospital records for all newly diagnosed diabetic patients arriving for the first consultation were maintained in the department. All patient level information available in register including age and gender of the patient, height and weight, blood pressure, triglyceride level, presence of proteinuria, measured intraocular pressure, severity of DR was extracted. At ophthalmology department, intraocular pressure was routinely measured with an air puff tonometer in all cases before pupillary dilatation with tropicamide plain/phenylephrine drops was performed. DR was evaluated and graded by an ophthalmologist using 90D lens and slit lamp for the presence of any retinal vascular abnormalities consistent with this entity – “dot-blot” hemorrhages, micro aneurysms, cotton-wool spots, intra retinal microvascular abnormalities, and/or venous beading. Additionally, DR staging and severity evaluation also included assessment of presence or absence of neovascularization. Patients were categorized to having either no DR, Nonproliferative Diabetic Retinopathy (NPDR; DR retinal manifestations without neovascularization), or Proliferative Diabetic Retinopathy (PDR; DR manifestations with any neovascularization) and were subdivided as mild, moderate and severe. Presence or absence of Diabetic Macular Edema (DME) was recorded while observing retina with 90D lens. DR severity for an individual patient was determined according to the staging of DR changes in the eye. Other abnormality related to the ocular manifestation of diabetes (corneal disease, cataract, glaucoma) was also recorded as ocular disease. Associated other medical history such as hypertension and hyperlipidemia were also noted and recorded as these are confounding diseases.\textsuperscript{10} Any family history of diabetes was also recorded. Newly diagnosed type 2 DM patients attending first ocular examination were included. Patients who had incomplete data in the hospital records, patients with type 1 diabetes, gestational diabetes, and patients...
presenting for first ocular examination after three months of diagnosis were excluded from the study. The authors were responsible for ophthalmic care to the patients and also extracted data for this study. Minimum number of patients required to draw meaningful conclusions was 60 which was estimated using a free online sample size calculator (for a 95% CI with a 10% margin of error assuming a DR prevalence of 19.3% \(^5\) in a newly diagnosed type 2 DM patients). The data was extracted in paper case report forms and entered into an Excel Worksheet. The data was analyzed using Statistical Package for Social Sciences (SPSS) Version 23. Descriptive statistics were computed and association between different demographic and clinical variables with DR was analyzed with chi-square test. To account for multivariate association of different clinical and demographic variables which are related to each other and also with DR in newly diagnosed DM patients, we performed a logistic regression analysis. A statistical significance level of p<0.05 was set for all analyses.

**Result**

Between Jan 2021 to Dec 2022, the ophthalmology department registered 102 cases of newly diagnosed type 2 DM who attended first ophthalmic evaluation. Patients with type 1 DM, gestational diabetes, attending first eye evaluation more than three months after initial diagnosis and whose records were incomplete in the ledgers were excluded. The mean age of patients at the time of the diagnosis was 49.1±14.0 \(^\text{y}\), 72(70.6%) were older than 40 \(^\text{y}\) and the youngest patient aged 30 \(^\text{y}\). There were more female 56(54.9%) patients in this cohort than males 46(45.1%). A family history of diabetes was present in 40(39.2%). Fifty(49%) patients were overweight or obese (BMI ≥25 kg/m\(^2\)) and 28(27.5%) patients had fasting hypertriglyceridemia. Elevated HbA1C levels of >6.5% at the time of presentation was recorded in 78(76.5%) patients; 15(14.7%) of patients had proteinuria on routine urinalysis. Additional ocular abnormality was identified in 33(32.4%) patients, Table 1.

At the time of diagnosis, 14(13.7%) patients were identified to have DR; mild PDR in 11(10.8%) and moderate PDR in 3(2.9%) patients was identified. Mean age was different in patients identified to have DR (56.6±15.1 \(^\text{y}\) and those without

| Table 1. Background characteristics of study population (N=102) |
|-----------------|-----------------|-----------------|
| Patient characteristics | N(%) | (Mean±SD) |
| Age in years [Mean ± SD] | 49.1±13.59 |
| Female | 56(54.9%) | - |
| Male | 46(45.1%) | - |
| Family history of diabetes | 40(39.2%) | - |
| Coexistence of any other ocular abnormality | 33(32.3%) | - |
| Systolic blood pressure [Mean±SD(IQR\(_{25-75}\))] | 124.6±16.3(120-130) |
| Elevated systolic blood pressure (≥140 mmHg) | 17(16.7%) | 79.9±9.8(70-90) |
| Diastolic blood pressure [Mean±SD(IQR\(_{25-75}\))] | 25.5±4.3(22.5-28.3) |
| Elevated diastolic blood pressure (≥90mmHg) | 26(25.5%) | 25.5±4.3(22.5-28.3) |
| Body mass index calculated (kg/m\(^2\)) [Mean±SD(IQR\(_{25-75}\))] | 8.3±2.4(6.5-10.1) |
| Overweight/obese (BMI≥25 kg/m\(^2\)) | 50(49%) | 78(76.5%) |
| HbA1C level at diagnosis [Mean±SD(IQR\(_{25-75}\))] | 141.5±60.8(105-171.2) |
| Serum fasting triacylglycerol at diagnosis [Mean±SD(IQR\(_{25-75}\))] | 28(27.5%) | 15(14.7%) |
| High fasting serum triglyceride level (≥150 mg/dl) | - | - |
| Presence of protein in urinalysis | - | - |
increasing age of the patient at time of the diagnosis with exception of significantly associated with presence of DR at most patient characteristics were not. The logistic regression model showed that characteristics were not, Table 2.

**Discussion**

In our study cohort of newly diagnosed type 2 DM patients, 14(13.7%) of patients had some evidence of DR. Most patients 72(70.6%) were older than 40 years with the mean age at the time of the diagnosis of diabetes being 49.13±14.00 years. When we compare this
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age with other hospital-based study done in Nepal\(^1\) that reported mean age of 57 years, our patients are diagnosed with diabetes at earlier age. The study was conducted in a tertiary eye hospital which is likely to receive patients with eye problems alone compared to a multidisciplinary hospital with in-house referral of the patient as in our series. Another study that evaluated awareness of DR among diabetic patients attending the vitreo-retinal service at a tertiary eye care center\(^6\) reported that fundus evaluation was done at the first consultation in only 48.6% of patients although almost four-fifths had diabetes of five years or more. In our study, all the cases were newly diagnosed patients with type 2 DM. This highlights that early referral and diagnosis of DR may be more efficient in multidisciplinary hospital.

In our study, 40(39.2%) patients had a positive family history of diabetes among which 8(20%) also had DR. However, 6(9.7%) patients whose family history of diabetes was negative also had DR. The role of genetic factors in shaping susceptibility to DR has been known for many years and family-based studies have indicated that DR susceptibility is heritable.\(^12\) Studies show that depending on the DR phenotype and ethnic population examined, siblings and relatives of diabetic patients with DR have approximately a 2 to 3 fold risk of DR compared with relatives of diabetic patients without DR and the degree of familial aggregation is greater for more severe forms of retinopathy.\(^12\) Heritability has been estimated to be as high as 27% for DR and 52% for PDR, a more advanced form of the disease.\(^12\) All of this evidence demands an early retinal examination of diabetes patients, if a family history exists and careful fundus evaluation is important if the patient has a positive family history of diabetes.

In our study, 50(49%) were overweight or obese (BMI ≥25 kg/m\(^2\)) and 28(27.5%) had fasting hypertriglyceridemia. Eight(16%) patient among obese individuals and 6(11.5%) among those with normal BMI had DR. The association between obesity and DR risk was reported in several previous observational studies, and a meta-analysis of prospective cohort studies was done to see the association of obesity and risk of DR in diabetes patients, obesity was associated with a significant increase in DR incidence (relative risk (RR), at 95% CI was 1.20 (1.01-1.43); \(I^2=59.6\)%.\(^13\) Our study, being a retrospective study, generates lower level of evidence than meta-analysis and the results did not reach statistical significance. However, high level of evidence for the existence of the relationship between obesity and DR underscores importance of a prospective study in future. Regarding the blood cholesterol level, elevated cholesterol and low-density lipoproteins (LDL) have also been linked to higher rates of hard retinal exudates in DME. In Early Treatment Diabetic Retinopathy Study (ETDRS) report, stated that patients with high total cholesterol and LDL levels were more likely to have retinal hard exudates compared to patients with normal lipid profiles.\(^14\)

Therefore, monitoring the treatment of serum lipids is beneficial in the management of DR.

Most patients, 78(76.5%) had elevated HbA1c levels of >6.5% at the time of presentation and 13(16.7%) had DR. In contrast, only 24(23.5%) of patients had levels <6.5% and only 1(4.2%) of them had DR. It is believed that the aggregation rate of red blood cells has a significant impact on the level of HbA1c. When the level of HbA1c in patients with diabetes is higher, a large number of red blood cells in the body will gather with each other at a faster speed, making fundus micro-vessels easy to form thrombus, which is the pathophysiological basis of early DR. Patients with persistently high HbA1c levels have poor blood glucose control and a significant increase in basal metabolic rate, resulting in a significant increase in tissue oxygen demand, which makes their tissues often in a state of hypoxia. At the same time, there is a kind of glycosylated hemoglobin with high affinity to oxygen in erythrocytes, which can prevent hemoglobin from binding to 2,3-Diphosphoglycerate (2,3-DPG), which makes the oxygen not easy to dissociate, resulting in tissue hypoxia and the proliferation of vascular growth factor, which is the basis of.
the occurrence and progression of diabetic retinopathy.\textsuperscript{15} It has been reported in various studies that there is a significant correlation between the incidence of DR and the level of HbA1c. They have found that type 2 diabetic patients with higher HbA1c levels have a significantly higher prevalence rate of retinopathy than diabetic patients with normal HbA1c and when HbA1c ≥7.0%, the incidence of retinopathy is about 85%.\textsuperscript{16} Therefore, attaining the standard of HbA1c can improve or delay the development of DR.

While evaluating other target organ damage by analyzing urine protein, we found that 15(14.7%) of total patients had proteinuria on routine urinalysis. The glomerular apparatus in diabetes patients shows widespread loss of podocytes and capillary occlusion, causing proteinuria and a decline in renal function.\textsuperscript{17} Urine Polymerase Chain Reaction (PCR) is largely used to diagnose diabetic kidney disease, study showed that diabetics with higher urine PCR levels had advanced stages of retinopathy thus suggesting all diabetics with increasing PCR should have a periodic retinal examination to prevent or retard the progression of DR.\textsuperscript{18} Proteinuria in a diabetes patient suggests a long duration of DM and hypertension; in our study patients with systolic hypertension were more likely to have at least mild DR at diagnosis than those who did not have systolic hypertension 9(10.6%) vs 3(11.5%). As proteinuria is caused by both the diseases, the association of the same with DR is inconclusive and demands urine PCR test in future studies.

In our study, at the time of diagnosis, 14(13.7%) patients were identified to have DR. The severity was classified as mild PDR in 11(10.8%) and moderate PDR in 3(2.9%) of patients. No severe DR was identified at the time of diagnosis of type 2 DM. Our study is similar to other studies where, in newly diagnosed type 2 DM participants, retinopathy occurred in 31(15.81%) of cases in a hospital-based study in Pakistan.\textsuperscript{19} In another retrospective review of all clinical records from the initial presentations of diabetic patients at the Tilganga Institute of Ophthalmology (TIO) from 2012 to 2014, 19.4% at the time of initial presentation had DR among which, 1305(14.7%) of which had NPDR, while 617(6.9%) demonstrated DME and 409(4.6%) demonstrated PDR.\textsuperscript{20} If we see the population-based study, observational population-based based on fundus photograph study researchers have observed up to 13% of individuals with type 2 diabetes have DR at the time of diagnosis. The majority of DR in these participants was mild NPDR (12%), but 0.6% of participants had moderate DR and 0.3% had PDR.\textsuperscript{21}

There are several limitations of this study and the results should be interpreted with these limitations. This was a hospital based study which only evaluated patients that were diagnosed with type 2 DM in medical outpatient clinic and attended the ophthalmology OPD. Many patients may not have attended eye clinic because of absence of eye symptoms that could have significantly changed the prevalence of DR at diagnosis. The generalizability of the results to the whole population is therefore limited. The data was collected retrospectively from hospital records with inherent limitations of hospital records for patient level data. There was no mechanism to control misclassification bias in patient characteristics and omission of other important confounding variables that could change the outcome in the hospital records. The number of patients included in the analysis was small which could have resulted in failure to demonstrate significant relationships with known risk factors of DR in the study population.

**Conclusion**

Diabetic retinopathy is already present in significant proportion of newly diagnosed type 2 DM patients. Routine screening for DR at the time of diagnosis can improve ocular outcomes in newly diagnosed diabetics with targeted early treatment. Future research should evaluate this is wider population to generate guidelines for need of mandatory eye evaluation at diagnosis.
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Conflict of Interest
None

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Reference