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RESEARCH ARTICLE
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ASSOCIATION BETWEEN SEVERITY OF DIABETIC RETINOPATHY WITH BIOMARKERS: A CROSS-SECTIONAL STUDY FROM A TERTIARY EYE HOSPITAL OF NEPAL

Dr. Lily Rajbanshi[1], Dr. Nistha Shrestha[2*], Dr. Sristi Thakur[3]

[1]Assistant Professor, Ophthalmologist / Vitreo Retina Consultant and Phaco Surgeon, Biratnagar Eye Hospital, Biratnagar, Nepal.
[2*]Ophthalmologist / Vitreo - Retina Fellow, Biratnagar Eye Hospital, Biratnagar, Nepal.
[3]Ophthalmologist / Vitreo Retina Fellow, Biratnagar Eye Hospital, Biratnagar, Nepal.

***Corresponding Author:** Dr. Nistha Shrestha
*Ophthalmologist / Vitreo - Retina Fellow, Biratnagar Eye Hospital, Biratnagar, Nepal.

ABSTRACT

Background

Diabetic Retinopathy is a chronic microvascular complication of diabetes mellitus. Several risk factors are associated with the development of diabetic retinopathy. This study aimed to investigate the associations of the severity of diabetic retinopathy with different biomarkers among patients with Diabetic Retinopathy.

Methods

A cross-sectional study involved 88 patients aged 40 years and older. Patients with a confirmed diagnosis of diabetic retinopathy resulting from Type 2 Diabetes mellitus were enrolled in the Vitreo-Retinal clinic of Biratnagar Eye Hospital of Nepal from April 2022 to April 2023. The diabetic retinopathy status of each patient was assessed through a comprehensive ophthalmologic examination, and grading of diabetic retinopathy was done. The duration of Diabetes mellitus, Glycosylated Hemoglobin levels, fasting blood sugar, postprandial, and several biomarkers (serum cholesterol, triglyceride, low-density lipoprotein, creatinine) of each participant were recorded and associations between the severity of DR and the duration of DM, HbA1c levels, and these biomarkers were explored**.**

Results

The mean age (mean ± SD) of 88 participants was 56.01 ± 9.09, with males being 69.3% of participants. According to the DR severity grading, 52.3% had Proliferative DR followed by 26.1% with severe non-proliferative DR, 14.8% with moderate non-proliferative DR, and 6.8% with mild non-proliferative DR. The vast majority (85.2%) of the patients had HbA1C levels higher than 7.0 mmol/l. There were significant associations between the severity of DR and HbA1C levels ($p = 0.022$) and between proliferative DR and uncontrolled fasting blood sugar levels ($p=0.001$). The duration of DM also exhibited a significant risk factor for the severity of DR ($p = 0.001$). No other biomarkers were found to have a significant association with severity of DR (all, $p \geq 0.05$).

Conclusions
HbA1c levels, duration of DM, and uncontrolled fasting blood sugar levels were strongly associated with the presence and severity of DR. Findings suggest that diabetic patients with higher HbA1C, indicating uncontrolled blood sugar for a prolonged period, are at risk of developing severe DR. This study recommends regular and comprehensive eye examination in patients with Type 2 DM to avoid the late presentation of severe DR and to prevent visual impairment.

Keywords: Diabetes mellitus**,** Diabetic retinopathy, Glycosylated Hemoglobin, Biomarkers, Nepal.

INTRODUCTION

Diabetic retinopathy (DR) is the most common microvascular complication in patients with diabetes mellitus (DM).[1]
Elevated Glycosylated Hemoglobin (HbA1c) reflects poorly controlled diabetes, which is one of the major causes of complications in DM including DR.[2]
High lipid levels are known to cause endothelial dysfunction due to a reduced bioavailability of nitric oxide. This endothelial dysfunction was suggested to play a role in retinal exudate formation in DR.[3]
The presence of a pre-existing microvascular complication (retinopathy or nephropathy) may contribute to the development of another.[4]
Nepal faces healthcare challenges, including limited eye care and diabetes management. Research linking DR severity to biomarkers is limited. A study conducted in a tertiary hospital could enhance policies, screening procedures, and interventions.
This study focuses on examining the association between key clinical parameters/biomarkers—glycated hemoglobin (HbA1c), duration of diabetes, fasting and postprandial blood sugar levels, lipid profile, and serum creatinine—and the risk of developing diabetic retinopathy.

MATERIALS & METHODS

This descriptive study included 88 participants aged 40 years and older. Participants were recruited from the existing database of diabetic patients who visited the Vitreoretinal Clinic of Biratnagar Eye Hospital for eye examination. Ethics approval was obtained from the Human Research Ethics Committee of Biratnagar Eye Hospital. The study followed the tenets of the Declaration of Helsinki.
Patients with a confirmed diagnosis of Type 2 DM and DR were included in this study. All the patients who visited Vitreoretinal Clinic had undergone a complete eye examination by retina specialists; anterior segment examination by a slit lamp biomicroscope and dilated posterior segment examination (with 0.5% tropicamide and 5% phenylephrine eye drops) by a fundus biomicroscope (using +90 D or +78 D) or binocular indirect ophthalmoscopy (using +20 D), as required. The inclusion criteria were patients with type 2 DM with diabetic retinopathy changes. The patients with type 1 DM, post-cataract/ vitrectomy surgery, pregnancy, hazy media, glaucoma, retinal Vaso-occlusive disease, Age-related macular degeneration, and renal diseases were excluded.
Patients with evidence of diabetic retinopathy were graded according to the International Clinical Diabetic Retinopathy Severity Scale [5].The severity of DR was classified by the International Clinical Diabetic Retinopathy Disease Severity Scale into five stages (no apparent DR, mild non-proliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, and proliferative diabetic retinopathy (PDR). Given there was a less number in each category of patients without PDR, for the analyses purpose, all patients were classified into two groups: NPDR and PDR. DR severity for an individual patient was determined according to the staging of the eye with the most severe disease manifestations.
The duration of diabetes mellitus was defined as the time interval in years between the date of the first diagnosis of DM and the date of the present evaluation. The levels of Hb1C, fasting and post-prandial blood sugar and other biomarkers, including serum lipoprotein and serum creatine were recorded from the medical records of each patient. The values of Hb1C and each biomarker were noted from the most recent laboratory tests results.

Assessment of glycemic control

Glycemic control was evaluated by testing HbA1C level using the gel precipitation method. Grading was done as controlled group HbA1C level < 7% and uncontrolled group HbA1C level >7 % by referring to American Diabetes Association guidelines[6].

Measurement of fasting (65-110 mg/dL) **and post-prandial blood sugar (**65-140 mg/dL)

Grading was done as controlled fasting blood sugar level <110 mg/dL and uncontrolled fasting blood sugar levels if > 110 mg/dL and grading of controlled postprandial blood sugar level <140 mg/dL and uncontrolled fasting blood sugar levels if > 140 mg/dL[7].

Measurement of serum Lipoprotein

Hypercholesterolemia was diagnosed if the serum cholesterol level was ≥ 200 mg/dl. The serum triglyceride level was considered high if it was ≥ 150 mg/dl. The serum low-density lipoprotein (LDL) cholesterol was considered high if it was ≥ 130 mg/dl. The serum high-density lipoprotein (HDL) cholesterol level was considered low if it was < 40 mg/dl and was considered high if it was ≥ 60 mg/dl, according to ATP III guidelines[8].

Measurement of serum creatinine

The serum creatinine level was considered high if it was ≥ 1.2 mg/dl and was considered low if it was 0.6 mg/dl [9].

Statistical Package for the Social Sciences (SPSS) version 29.0 was used for data entry and analysis. Statistical significance was tested by using Chi-square test where indicated. Statistical significance (p value) was set at < 0.05.

RESULTS

A total of 88 patients majority (72.7%) were than 50 years of age group. Males were high (69.3%), the majority (38.6%) were of more than 10 years of DM, 59.1% had normal cholesterol level, 80.7% had normal HDL, 77.3% had normal LDL, 58% had normal triglycerides and 85.2% had normal serum creatinine level, only 14.8% had controlled fasting blood sugar, 12.7 had controlled Post prandial blood sugar level and 85.2% had HbA1c level higher than 7.

Characteristics	**Number (%)**
Age Group	
<50	24 (27.3)
≥50	64 (72.7)
Gender	
Male	61 (69.3)
Female	27 (30.7)
Duration of DM	
1-5 years	25 (28.4)
6-10 years	29 (33)
>10 years	34 (38.6)
Cholesterol Level (mg/dL)	
Normal (< 200)	52 (59.1)
High (≥ 200)	36 (40.9)
Serum HDL (mg4/dL)	
Normal (40-60)	66 (75.0)
High (≥ 60)	9 (10.2)
Low (≤ 40)	13 (14.8)
Serum LDL (mg/dL)	

Normal (< 130)	68 (77.3)
High (≥ 130)	20 (22.7)
Triglycerides (mg/dL)	
Normal (< 150)	51 (58)
High (≥ 150)	37 (42)
Serum creatinine (mg/dL)	
Normal (0.6-1.4)	75 (85.2)
High (≥1.4)	13 (14.8)
Fasting Blood Glucose Level (mg/dL)	
Control (<110)	13 (14.8)
Not Control (≥ 110)	75 (85.2)
Post Prandial Blood Glucose Level (mg/dL)	
Control (<140)	11 (12.5)
Not control (≥ 140)	77 (87.5)
HbA1c level (%)	
< 7	13 (14.8)
≥7	75 (85.2)
Total	**88 (100)**

Table 1: Demographic Characteristics of the patients (n=88)

The majority (52.3%) had PDR, followed by 26.1% severe NPDR, 14.8% moderate NPDR, and 6.8% had mild NPDR respectively.

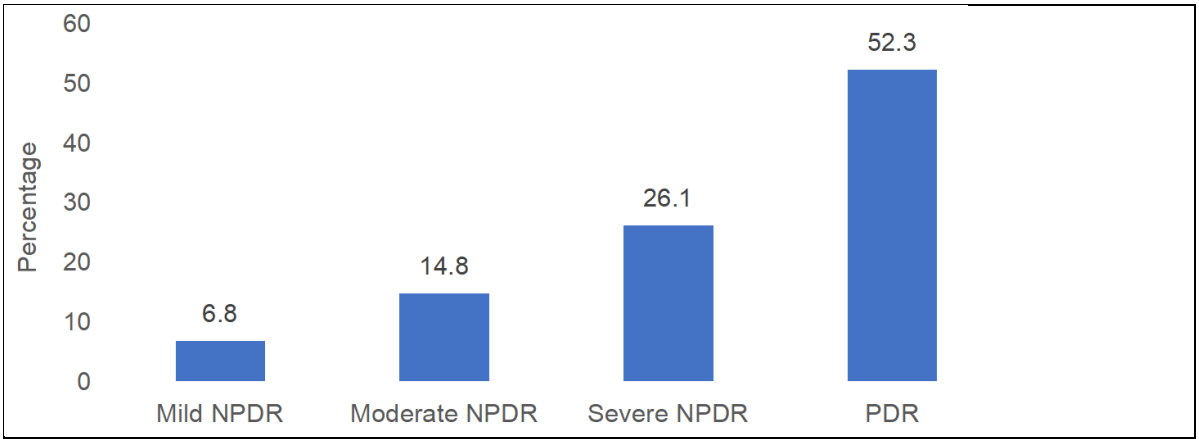

Figure 1: Distribution of patients with Severity of Diabetic retinopathy in the worse eye

Notably, there was a statistically significant association with the severity of DR with a duration of DM, fasting blood sugar level, and HbA1c level (p value<0.05). There was no statistically significant association with the severity of DR with age group, gender, cholesterol level, triglycerides, and serum creatinine level.

Characteristics	NPDR (%)	PDR (%)	Number of cases	p value
Age Group				
<50	41.70	58.30	24	0.486
≥50	50.00	50.00	64	
Gender				
Male	41.00	59.00	61.00	0.057
Female	63.00	37.00	27.00	
Duration of DM				

1-5 years	64.00	36.00	25	0.001
6-10 years	62.10	37.90	29	
>10 years	23.50	76.50	34	
Cholesterol Level (mg/dL)				
Normal (<200)	46.20	53.80	52	0.722
High (≥200)	50.00	50.00	36	
Serum HDL (mg/dL)				
Normal (40-60)	73.80	76.10	66	0.249
High (≥ 60)	9.50	10.90	9	
Low (≤ 40)	16.70	13.00	13	
Serum LDL (mg/dL)				
Normal (<130)	47.10	52.9	68	0.817
High (≥ 130)	50.00	50.0	20	
Triglycerides (mg/dL)				
Normal (<150)	49.00	51.00	51	0.776
High (≥150)	45.90	54.10	37	
Serum creatinine (mg/dL)				
Normal (0.6-1.4)	50.70	49.30	75	0.185
High (≥ 1.4)	30.80	69.80	13	
Fasting Blood Glucose Level (mg/dL)				
Control (< 110)	92.3	7.7	13	0.001
Not Control (≥ 110)	40	60	45	
Post Prandial Blood Glucose Level (mg/dL)				
Control (< 140)	72.7	27.3	11	0.076
Not control (≥ 140)	44.2	55.8	77	
HbA1c level (%)				
< 7	76.90	23.10	13	0.022
≥7	42.70	57.30	75	
Total	**47.70**	**52.30**	**88**	

Table 2. Association of Severity of Diabetic Retinopathy with HbA1c and other biomarkers

DISCUSSION

Our study found that the severity of diabetic retinopathy was statistically associated with HbA1c level and duration of diabetes, which was similar to other studies.[10] More than half of the patients had PDR, which was much higher than the study done by Almutairi NM [10] and Pakistan study.[11] This may be due the fact that the Biratnagar eye hospital is a tertiary eye care center, and the majority of advanced eye diseases are referred to the retina department and also access to healthcare services, including eye care facilities, is limited, particularly in rural areas. This can lead to delayed diagnosis and treatment of diabetic retinopathy. Lack of regular screenings and access to specialized treatment can result in advanced stages of retinopathy, including PDR, being more common when the condition is finally detected.[12]

In Nepal, challenges such as affordability of medications, limited access to healthcare professionals, and cultural factors affecting diet and physical activity patterns, sedentary lifestyles can impact diabetes management outcomes.[13]

Therefore, Addressing the high number of PDR in Nepal requires a multifaceted approach including improving access to healthcare services, increasing awareness about diabetes and its complications, enhancing diabetes management programs, and promoting early detection and treatment of diabetic retinopathy through regular screenings.

The Early Treatment Diabetic Retinopathy Study (ETDRS) identified HbAlc as one of the most important risk factors for the progression to high-risk proliferative retinopathy.[14]

Our study found that hyperglycemia, as measured by HbA1c, is a significant risk factor associated with the severity of DR and showed PDR patients with values higher than 7 had poor glycemic control and experienced disease worsening. In this study, the mean HbA1c level of the patients was 9.1 (SD = 2.2) which suggests most of the patients have uncontrolled diabetes mellitus. In CURES-I study, for every 2% elevation of HbA1c, the risk for DR increased by a factor of 1.7 (95% CI: 1.545–1.980; $P < 0.0001$).[15,16] Our results showing a significant association between HbA1C levels and severity of diabetic Retinopathy are consistent with other reports.[14,16,17]

Most of the study subjects with diabetic retinopathy 64 (72.7%) were above 50 years of age. The male population exceeds the female population in terms of gender distribution. This could be due to a recent trend of increased diabetic prevalence in males due to biological factors (such as differences in fat distribution and hormonal influences) as well as lifestyle factors (such as higher rates of smoking, alcohol consumption, and less healthy dietary habits), increased level of awareness, and males have better access to healthcare facilities due to factors such as greater mobility than females in the Nepalese society, societal norms that prioritize male health care-seeking behavior, and economic factors where males are more likely to be the primary earners.[13]

In the present study, glycosylated hemoglobin level (HbA1c), fasting blood sugar (FBS), post-prandial blood sugar (PPBS) were raised predominantly in patients with diabetic retinopathy which is comparable to the study conducted in Chitwan medical college[17] and in Pakistan study.[11]

This study found that the overall presence of retinopathy increases as the duration of DM increases. The incidence of retinopathy also increases with increasing duration. Klein R and et al reported that 10 years after the diagnosis of type 2 diabetes, 67% of patients had retinopathy and 10% had PDR.[18] Our findings were similar to other hospital-based and population-based studies in Nepal and other countries.[19,20]

In this study, all four serum lipoproteins (LDL, Triglyceride, HDL, and total cholesterol) were measured and there was no statistically significant association of these indicators with DR, and the results are similar to the study conducted by Kiran et al[21]. Similarly, The United Kingdom Prospective Diabetes Study showed no association between triglyceride levels, LDL, and the progression of diabetic retinopathy.[22] But in contrast to study done at Nepal showed significant association.[19]

In our study, the higher serum creatinine level was not statistically significant with DR. However, another study showed that Higher serum creatinine was another risk factor for DR.[20, 23]

Research has shown that higher levels of serum creatinine are linked to an increased risk of progression of sight-threatening diabetic retinopathy. In summary, monitoring serum creatinine levels is essential for assessing kidney function and understanding its impact on diabetic retinopathy. Regular check-ups and early intervention are crucial for managing both conditions[24]. A holistic approach should aim to control the modifiable risk factors like blood sugar, blood pressure, lipid profile, kidney function, and obesity to prevent DR.[19]

Our study can contribute to enhancing the understanding of the link between Diabetic Retinopathy and its associated risk factors. This could help patients and doctors recognize the importance of regular visits to the Ophthalmologist for early detection and better management of the disease.

LIMITATION OF THE STUDY

The limitation of the study is that we were unable to assess the proteinuria/ albuminuria of the participants for the analysis of risk factors of DR.

CONCLUSION

The severity of Diabetic retinopathy increases with higher HbA1c and longer duration of diabetes, poor level of glycaemic control. Therefore, Early detection, timely ocular treatment, and good control of the underlying risk factors are the keys to reducing blindness due to DR.

Conflict of Interest: None

LIST OF ABBREVIATIONS

DM=Diabetes Mellitus
DME=Diabetes Macular Edema
DR=Diabetic Retinopathy
HbA1c=Glycosylated hemoglobin
ADA=American Diabetes Association
FPG=Fasting plasma glucose
OGTT=Oral glucose tolerance test
NPDR=Non-proliferative diabetic retinopathy
PDR=Proliferative diabetic retinopathy
HDL=High-density lipoprotein
LDL=Low-density lipoprotein
SPSS=Statistical Package for the Social Sciences
ETDRS=Early Treatment Diabetic Retinopathy Study
FBS=Fasting blood sugar
PPBS=post-prandial blood sugar
WHO=World Health Organization

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