Original Article

Burden and Risk Factors of Diabetic Retinopathy Among Diabetic Patients Attending a Multispecialty Tertiary Eye Hospital in Nepal

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ABSTRACT

Introduction: As the number of people with diabetes mellitus is increasing because of urbanization and change in dietary habits and sedentary lifestyle, the number of diabetic retinopathy is also expected to increase in future. [1] [sa2] We aimed to find out the prevalence of diabetic retinopathy and associated risk factors among diabetic patients in the tertiary eye hospital.

Materials and methods: This is the observational cross-sectional study enrolling 420 diabetic patients visiting the multispecialty tertiary eye hospital between March 2020 and February 2021. Anthropometry measurement, laboratory risk profiles and blood pressure were recorded

Results: The prevalence of any diabetic retinopathy, proliferative diabetic retinopathy, and diabetic macular edema were 30.96 %, 6.19 %, and 5.95 % respectively. The duration of DM (p=0.001), hypertension (p=0.04), high SBP (p=0.023), abdominal obesity (p=0.015), high LDL(p=0.011) cholesterol, low HDL cholesterol(p=0.012), and creatinine (p=0.001) were associated with DR in our study.

Conclusion: A holistic approach should target to control the modifiable risk factors like blood sugar, blood pressure, lipid profile, kidney function, and obesity to prevent DR. Anthropometric assessment of waist to height and waist circumference should be included in the holistic health promotion strategy in Nepal as BMI may not be risk factors for DR in Nepalese people.

Key words: Burden, Diabetic retinopathy, Nepal, Risk factors.

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Conflict of Interest : Nil

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INTRODUCTION

One meta-analysis revealed the urban prevalence of type 2 diabetes mellitus to be 8.1%, and rural prevalence of 1.0 % in Nepal (Gyawali *et al.*, 2015). Further, type 2 diabetes mellitus prevalence is predicted to climb secondary to lifestyle and urbanization changes(Vaidya *et al.*, 2005). Diabetic retinopathy (DR) is amongst the most common microvascular complications due to diabetes. It is the foremost reason for vision impairment and blindness within the economically remunerative working-age population globally (Yau *et al.*, 2012). Different hospital-based surveys depicted a prevalence of DR from 20.31% to 78% in Nepal(Shrestha and Gurung, 2007; Shrestha *et al.*, 2007; Shrestha, 2011; Thapa *et al.*, 2012; Poudyal *et al.*, 2019).

So far, three crucial modifiable risk factors; hypertension, hyperglycemia, and dyslipidemia are evident risks of all DR endpoints(Yau *et al.*, 2012; ICO Guidelines and Care, 2017). In addition, every 10% decrease in HbA1C is associated with a 42% decline in the risk of retinopathy progression. Further, each 10% increase in HbA1C, leads to the risk of retinopathy progression by 64%. Moreover, the American Diabetes Association suggests a goal of less than 7.0 % to secure upon the risk of DR(International Council of Ophthalmology, 2017). For diabetic patients, the relative risk of DR is to have hypertension by 1.7 folds. Additionally, for each 10 mmHg rise in systolic blood pressure, there were 1.23 times rise in the risk of DR and 1.19 times for the risk of vision-threatening DR(Zheng *et al.*, 2012).Higher levels of cholesterol, serum triglycerides, and low-density lipoproteins have been related for causative for diabetic macular edema in accordance to a meta-analysis(Atchison and Barkmeier, 2016). On the contrary, behavioral risk factors like alcohol and smoking with DR are debated(Young *et al.*, 1984; Moss, 1991; Zhu *et al.*, 2016). Nevertheless, these habits should not be promoted from an overall health protection perspective in Nepal. Inadequate physical exercise is also resulting in obesity as the next modifiable risk factors for both DM and DR(Dirani *et al.*, 2011; Garoma, Merga and Hiko, 2020).Besides, increased body mass index (BMI) is associated with an rising risk of DR(Guidelines and Care, 2017). However, some reports have inverse relation among higher BMI and DR (Lim *et al.*, 2010; Rajiv *et al.*, 2010). Thus, there is a necessity to explore these areas in Nepal.

Here, we aim to analyze the burden of DR and risk factors at BP Eye Foundation, Hospital for Children, Eye, ENT and Rehabilitation Services (CHEERS), the tertiary eye hospital located in Bhaktapur district in Nepal.

MATERIALS AND METHODS

This cross-sectional study enrolled 420 diabetic patients CHEERS from March 2020 to February 2021. We excluded patients with a history of gestational diabetes mellitus. We obtained approval to conduct the study from the Ethical review board of Nepal Health Research Council and followed the tenets of the Helsinki declaration. Trained Ophthalmic Assistants obtained informed consent for the participants before enrolling in the study. Then

ophthalmologists screened the diabetic patients. A detailed questionnaire was filled to obtain information, including demographic profile, duration, family history of diabetes, associated hypertension, current smoking and alcohol intake status, medical history and medication use.

We used a slit lamp biomicroscope (SLB) for anterior segment examination. Either Volk 78/90 diopter assisted by SLB or 20 diopter convex lens coupled with head mounted binocular indirect ophthalmoscope was used to evaluate the posterior segment finding after dilating patients' eye with 1% Tropicamide and 2.5 % Phenylephrine eye drop and with 1% Tropicamide for hypertensive patients. Grading of DR was confirmed by retina specialists according to the International Classification of Diabetic Retinopathy and Diabetic Macular Edema scale (Guidelines and Care, 2017).

BMI cut-off points in the Asian population by World Health Organization (WHO) were used for defining obesity. Individuals with BMI below 18.5 were categorized as underweight, from 18.5 to 22.9 as healthy, 23 to 26.9 as overweight, and above 27 as obese. Abdominal obesity was defined as a waist circumference of 90 cm in men and 80 cm in women and waist to height ratio of 0.6 or more (WHO, 2004). Fasting blood sugar 126 mg/dl or more, postprandial blood sugar of 200 mg or more, HbA1c 6.5 or more, patients under Insulin or hypoglycemic treatment or patients self-report as diabetes was labeled as a diabetic patient (American diabetic association, 2010).Type 1 and Type 2 DM was labeled according to the physicians note on the type of DM. Systolic blood pressure of 140 mm of Hg or more and diastolic blood pressure of 90 mm of Hg or more self-reported hypertension was considered hypertension (Benetos *et al.*, 2017).

Data Entry and Statistical Analysis: Data entry was secured with EpiData version 3.1, from the EpiData Association of Denmark (www.epidata.dk). Data were summarized as frequency, percentages, mean and 95% Confidence Interval (CI) for the variables. Chi square test and univariate analyses with crude OR and adjusted OR were used to see the association between DR and risk factors. A p-value of <0.05 was considered statistically significant. Adjusted OR was calculated using binary logistic regression putting the variables with $p<0.1$ in the model.

RESULTS

Type 2 diabetic patients comprised 94.5 %. Eighty-five percent of diabetic patients were taking oral hypoglycemic medications and Insulin. Only 7.1 % of patients with DM responded to the positive family history, while 42.1 % of patients were not aware of diabetic family history. Forty-five % of patients with DM had concomitant Hypertension. More than 16 % of patients were current smokers and 7 % of patients were currently alcoholics. More than 50 % of patients had a sedentary or lightly active lifestyle (Table 1).

Almost 31 % of diabetic patients had some form of retinopathy,24.03% had NPDR, 6.19 % had PDR and 5.95 % had DME (Table 2).

Table 1: Clinical and behavioral history characteristics of participants (n=420).

Characteristics		Frequency	Percentage
Type of diabetes	Type 1	23	5.5
	Type 2	397	94.5
Duration of diabetes	< 5 Years	157	37.4
	5-10 years	95	22.6
	>10 years	168	40
Treatment of diabetes	Observation	16	3.8
	Dietary control	15	3.6
	Herbal medicine	8	1.9
	Allopathic medicine	306	72.9
	Insulin	51	12.1
	No treatment	24	5.7
Family history of diabetes	Yes	30	7.1
	No	213	50.7
	Don't know	177	42.1
History of hypertension	Yes	191	45.5
	No	229	54.5
Smoking habit	Never	279	66.4
	Current	69	16.4
	Past smoker	71	16.8
Alcohol habit	Never	363	86.4
	Current	29	7.0
	Past	28	6.6
Physical activity habit	Sedentary or lightly active	226	53.8
	Active	194	46.2

Table 2: Diabetic retinopathy grading among the participants (n=420).

Diagnosis based on worse eye	Frequency	Percentages
No DR	290	69.04
Any retinopathy	130	30.96
Mild NPDR	51	12.14
Moderate NPDR	32	7.61
Severe NPDR	18	4.28
PDR	26	6.19
DME Central	20	4.76
DME Non Central	5	1.19

DR= diabetic retinopathy; NPDR= non proliferative diabetic retinopathy; PDR= proliferative diabetic retinopathy; DME= diabetic macular edema

Table 3: Diabetic retinopathy prevalence in various studies in Nepal and Asia.

Country (study by)	Year	Setting	DR Prevalence (%)	PDR Prevalence (%)	DME Prevalence (%)
Nepal, Poudyal G et al[5]	2019	Hospital	19.4	4.6	6.9
Nepal, Thapa R et al[26]	2014	Hospital	38.26	2.52	5.78
Nepal,Agrawal L et al[27]	2018	Community	15.3	1.4	2.1
Nepal,Pokharel SM et al[28]	2015	Community	38.8	3.8	1.9
Nepal, RK Shrestha et al[7]	2011	Hospital	20.31	7.03	-
Nepal, Thapa R et al[8]	2012	Hospital	77.6	16.67	36.7 %
Nepal, Mishra SK et al[17]	2016	Population	10	0.5	5.5
Bangladesh, Muqit MMK et al[29]	2019	Hospital	33	7.8	10.9
India, Rajalakshmi R etal[29]	2020	Hospital	32.3	10.7	9.1
Myanmar,Patel S et al[29]	2017	Hospital	34	13.5	-
Thailand, Chetthakul T et al [29]	2015	Community	31.4	9.14	-

Prevalence study of DR in Nepal and Asia is summarized at table 3.

The duration of DM (p=0.001), hypertension (p=0.04), high SBP (p=0.023), abdominal obesity (p=0.015), high LDL (p=0.011) cholesterol, low HDL cholesterol (p=0.012), and creatinine (p=0.001) were associated with DR in our study. Odds of getting DR are almost three times when duration of DM is less than 5 years versus 5- 10 years, which further increases to nearly ten times when duration of DM increases to more than ten years (Table 4).

Table 4: Risk factors of diabetic retinopathy.

Characteristics		DR		χ2 p value	Odds CI 95 %
		No n (%)	Yes n (%)		
Gender	Male	151 (55.8)	75 (33.2)	0.124	1.39 (0.91-2.13)
	Female	141 (73.7)	51 (26.3)		1
Duration (Years)	< 5	130 (89.7)	15 (10.3)	<0.001	2.97 (1.46-6.03)
	5-10	70 (74.5)	24 (25.5)		9.19 (4.98-16.99)
	>10	82 (48.5)	87 (51.5)		1
Hypertension	No	172 (74.1)	60 (25.9)	0.040	1
	Yes	122 (64.9)	66 (35.1)		1.55 (1.02-2.36)
Smoking	No	28 (63.6)	16 (36.4)	0.823	1.10 (0.46-2.65)
	Yes	29 (65.9)	15 (34.1)		1
Alcohol	No	138 (66.0)	71 (34.0)	0.678	1.18 (0.53-2.62)
	Yes	23 (69.7)	10 (30.3)		1
SBP (mmHg)	>=140	93 (62.4)	56 (37.6)	0.023	1
	<140	176 (73.3)	64 (26.7)		1.66 (1.07-2.57)

DBP(mmHg)	>=90	75 (68.2)	35 (31.8)		1
	<90	194 (69.3)	86 (30.7)	0.832	1.05 (0.65-1.69)
BMI	<27	206 (67.8)	98 (32.2)	0.105	1.49 (0.92-2.44)
	>=27	88 (75.9)	28 (24.1)		1
Waist to Height ratio	<0.6	117 (63.9)	66 (36.1)	0.015	1.73 (1.11-2.69)
	>=0.6	150 (75.4)	49 (24.6)		1
Waist circumference Female	<80	9 (60.0)	6 (40.0)	0.207	1
	=>80	120 (75.0)	40 (25.0)		0.50 (0.17-1.49)
Waist circumference male	<90	28 (53.8)	24 (46.2)	0.016	1
	=>90	108 (72.0)	42 (28.0)		0.45 (0.24-0.87)
FBS (mg/dl)	<126	206 (71.8)	81 (28.2)	0.243	1
	>=126	88 (66.2)	45 (33.8)		1.30 (8.4-2.02)
HbA1C(%)	<6.5	49 (65.3)	26 (34.7)	0.312	1
	>=6.5	78 (58.2)	56 (41.8)		1.35 (0.75-2.43)
Creatinine(mg/dl)	<1.2	121 (73.3)	44 (26.7)	<0.001	1
	>1=1.2	28 (45.2)	34 (54.8)		3.34 (1.82-6.13)
Total Cholesterol(mg/dl)	<200	107 (64.5)	59 (35.5)	0.556	1
	>=200	46 (60.5)	30 (39.5)		1.18 (0.68-2.07)
LDL(mg/dl)	<100	84 (71.8)	33 (28.2)	0.011	1
	>=100	70 (56.0)	55 (44.0)		2.00 (1.17-3.42)
TG(mg/dl)	<150	85 (63.4)	49 (36.6)	0.881	1
	>=150	74 (64.3)	41 (35.7)		0.96 (0.57-1.61)
HDL(mg/dl)	>60	129 (60.3)	85 (39.7)	0.012	1
	<=60	23 (85.2)	4 (14.8)		0.25 (0.09-0.79)

DR=diabetic retinopathy, HbA1C=glycated hemoglobin, FBS=fasting blood sugar, LDL=low density lipid, HDL=high density lipid, TG= triglycerides, SBP=systolic blood pressure, DBP=diastolic blood pressure, BMI=Body mass index, X^2=chi square, CI=Confidence interval, mmHg=millimeter of mercury, mg/dl=milligram/deciliter

DISCUSSION

Our study showed 94.5 % of diabetic patients were type 2 DM followed by 5.5 % of type 1 DM. Type 1 DM is less than 3 % in a yearly serial study done in another tertiary eye hospital in Kathmandu(Thapa *et al.*, 2014; Poudyal *et al.*, 2019)**.** Almost 31 % of diabetic patients had some form of DR, 6.19 % had PDR and 5.95 % had DME in our study. Although the prevalence of any DR in our study is slightly higher than the estimated national hospital-based prevalence of DR(19.4%), the prevalence of PDR and DME in our study is close to prevalence noted in the estimated national prevalence of PDR (4.6%) and DME (6.9%)in Nepal(Takkar *et al.*, 2021)**.** However, the prevalence of DR, PDR and DME varied from 15.3 to 77.6 %, 0.5 to 16.3 %, and 1.9 to 36.7 %, respectively, in studies from 2011

onwards in Nepal (Shrestha, 2011; Thapa *et al.*, 2012, 2014; Pokharel *et al.*, 2015; Mishra, Pant and Subedi, 2016; Agarwal and Agrawal, 2018; Poudyal *et al.*, 2019). The varied study designs, the selection bias, sampling size, setting, DR risk comorbidities, and health-seeking behavior among study participants might have introduced different prevalence of DR, PDR and DME within the country.

While compared to Asian context, this correlates to the prevalence of DR in India (32.3%), Myanmar(34%), Bangladesh(33%), Thailand(31.4%) and Sri Lanka(27.4%) (Takkar *et al.*, 2021). This also correlates most closely to the met-analysis report in global prevalence. In addition, overall prevalence appeared to be 34.6% for whatsoever DR, for proliferative DR 6.96%, for diabetic macular edema 6.81%, and for vision threatening diabetic retinopathy (VTDR) 10.2%(Yau *et al.*, 2012).

In our study, concomitant hypertension, duration of diabetes, abdominal obesity, creatinine level, high LDL and low HDL values were associated with risk factors for diabetic retinopathy. The advantageous effects of tight blood glucose control is proven to halt the progression of DR(Atchison and Barkmeier, 2016; International Council of Ophthalmology, 2017). The odds of DR increased by 1.5 times when there was concomitant hypertension and by 1.65 times when SBP more than 140 mmHg in this present study. The significant impacts of higher SBP and lower DBP on DR may indicate a role of large arteries stiffening. The relative risk of diabetic retinopathy is 1.7 for diabetic patient with concomitant hypertension(Wong *et al.*, 2008; Atchison and Barkmeier, 2016). Furthermore, a study found that for every ten mmHg increase in systolic blood pressure, there was 1.23 times increased risk of diabetic retinopathy and 1.19 times increased risk of vision-threatening retinopathy. For every 10 mmHg increase in diastolic blood pressure, there was a 0.71 relative risk of diabetic retinopathy and 0.65 relative risks of vision-threatening retinopathy. In addition, the UK Prospective Diabetes Study has shown that intensive blood pressure treatment in hypertensive subjects with Type 2 diabetes prevented or delayed progression of DR(Pradeepa *et al.*, 2008; Atchison and Barkmeier, 2016).

Abdominal obesity is also linked with DR in our study. Association of Obesity and DM as a part of metabolic syndrome and increased BMI has been linked to an increased DR risk in many studies(Lim *et al.*, 2010; Dirani *et al.*, 2011; Lee *et al.*, 2014; Atchison and Barkmeier, 2016). Despite that, not all studies have depicted an increased risk of DR in people obese patients with diabetes. Further, some studies have shown the paradoxical effect that BMI has a protecting effect from DR. In contrast, BMI and DR may not be associated with enrolling more type 1 DM as they have a different metabolic risk profile(Lim *et al.*, 2010; Atchison and Barkmeier, 2016). The waist-to-hip ratio has been described as an important index for abdominal obesity. It has been linked to significantly higher rates

of DR. Appealingly, increased neck and waist circumference is reported to be linked with both raised risk of and increased the severity of DR(Dirani *et al.*, 2011)**.** In our study, the reason for the lack of association with BMI is not clear; it may be that Asians are more likely to develop intra abdominal fat and that BMI may not be an accurate indicator of adiposity in Nepalese people. Diabetic patients with DR could have adopted more physical activities that helped to achieve a normal BMI level.

We also found high LDL and low HDL cholesterol were risk factors in DR. However, we did not have data of diabetic patients taking lipid-lowering agents. In a large meta-analysis, patients with DME tend to have higher total cholesterol levels, low-density lipoproteins, and serum triglycerides. Elevated cholesterol and LDL have also been linked to higher rates of hard retinal exudates in DME. Monitoring and treatment of serum lipids to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines of low-density lipoprotein cholesterol <100 mg/dl is a reasonable goal(Atchison and Barkmeier, 2016; Guidelines and Care, 2017; Zhang *et al.*, 2017)**.**

Interestingly, glycaemic level was not significantly associated with DR in our study. It could be possible that patients with high blood sugar might have presented earlier before DR and those with controlled blood sugar perhaps have been aware of the harmful consequences of DR despite presenting with DR. Nevertheless, we did not find the association of smoking and alcohol consumption habits in the occurrence of DR.

Higher serum creatinine was another risk factor of DR in our study. Both chronic kidney diseases (CKD) and DR share the frequent microvascular complications of long standing DM. Therefore, screening for DR may additionally inform on the necessity for further investigation into the etiology of kidney disease and on the severity of diabetes-related CKD and present an opportunity to prevent progression to kidney failure. Thus, this implies a positive diagnostic for one of these complications must have a prompt recommendation to assess the other(Ahmed Aziz, 2018; Park *et al.*, 2019; Pavkov *et al.*, 2019; Zhuang *et al.*, 2019)**.**

The strength of our study includes that DR is diagnosed and confirmed by the retina specialists, unlike simply fundus photo-based examination. We completed assessments of a wide range of risk factors, including serum biochemistry, blood pressure and anthropometric measurement. The study's main limitation is that it is a cross-sectional design, and the data may be confounded by survivor bias. Further, the next limitation of the study is that it is a hospital-based study; the patients recruited into our study may not represent the overall population with diabetes.

CONCLUSION

Hospital-based prevalence of diabetic retinopathy at Bhaktapur is 30.96 %. The

duration of diabetes, hypertension, abdominal obesity, high LDL cholesterol, low HDL cholesterol, creatinine is associated with diabetic retinopathy. Awareness campaigns should be focused from a holistic point of view addressing the importance of control of modifiable risk factors like optimum control of blood sugar, blood pressure, lipid profile, kidney function, and obesity to prevent DR. Higher BMI may not necessarily be a risk factor for DR in Nepalese population. Hence, anthropometric assessment of waist to height and waist circumference should be included in the holistic health promotion strategy in Nepal.

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