Association of HBA1c and Plasma Glucose Levels with Diabetic Retinopathy

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ABSTRACT

Background

Diabetic retinopathy is one of the leading causes of blindness worldwide. The relationship between glucose level and development of diabetic retinopathy has always been an area of interest and constantly evolving.

Objective

To determine the association of glycosylated hemoglobin and plasma glucose levels with different grades of diabetic retinopathy.

Method

A hospital based cross sectional study was conducted among 504 patients with type II diabetes mellitus attending the Department of Ophthalmology in a University Hospital for one year duration. Relevant history regarding diabetes mellitus was recorded for all patients. The status of diabetic retinopathy in each patient was diagnosed by detailed ophthalmological examination and classified according to International Classification of Diabetic Retinopathy Scale. All the patients were evaluated for their glycosylated hemoglobin, fasting and post prandial blood glucose levels. Bivariate analysis using t-tests and chi-square tests was used to measure the strength of association between the different variables. An Analysis of Variance (ANOVA) test was used to evaluate the association between the means of different variables.

Result

Total 504 patients constituted of 254 males (50.39%) and 250 (49.60 %) females. Almost half of the study population had poor glycemic control and deranged fasting and post prandial blood sugar levels. Diabetic retinopathy was observed in 124 (24.60%) patients and diabetic macular edema was observed in 42 (8.33%) patients. Poor control of glycosylated hemoglobin (> 7.6) was seen in 88 (70.96%) cases of diabetic retinopathy and 34 (80.95%) cases of diabetic macular edema. Uncontrolled fasting and postprandial blood sugar levels were associated with a significant number of cases of diabetic retinopathy and of diabetic macular edema respectively. A statistically significant association was observed between increasing grades of diabetic retinopathy and higher glycosylated hemoglobin and plasma glucose levels.

Conclusion

Higher the level of glycosylated hemoglobin and plasma glucose levels, more severe is the grade of diabetic retinopathy.

KEY WORDS

Diabetic retinopathy (DR), Fasting blood sugar, Glycosylated hemoglobin (HBA1c), Non-proliferative diabetic retinopathy (NPDR), Proliferative diabetic retinopathy (PDR),

INTRODUCTION

Diabetic retinopathy (DR) is a chronic progressive, potentially sight threatening disease of retinal microvasculature associated with prolonged hyperglycemia and constitutes 4.8% of blindness globally.[1,2] Landmark clinical trials and epidemiological studies among the diabetic patients have shown that optimal level of blood glucose control can prevent and delay the onset and progression of diabetic microvascular complications.[3-5] Since many years, diagnostic criteria of Diabetes mellitus (DM) have been based either on fasting blood glucose, two hours post prandial glucose or glycosylated hemoglobin (HbA1c) and reducing the HbA1c level has been considered most important target for the diabetes treatment. HbA1c is valued as best available biochemical parameter to assess the metabolic control of glucose in the previous 6-8 weeks and its estimation is directly proportional to blood glucose concentration.[6]

The relationship of blood glucose to retinopathy is significant as people with HbA1c levels less than 6.5% develop little or no retinopathy.[7]

Studies have claimed that there is 30-35% reduction occurs in microvascular complications per 1% reduction in HbA1c and 14-16% reduction in macrovascular complications for 1% deduction in HbA1c.[8] Some other studies have suggested that lowering the fasting and post-prandial blood glucose levels are important as controlling HbA1c levels for the prevention of vascular complications like diabetic retinopathy.[9-12] Such studies have been conducted worldwide extensively but in Nepal until now, no study has studied the associations of DR with HBA1c and plasma glucose levels in either hospital based or large population based settings. Thus, our study would bridge the gap and provide basic data evaluating the association between plasma glucose levels, glycosylated hemoglobin levels with diabetic retinopathy which would aid in conducting further large population based studies in Nepal. Data thus obtained can be utilized for planning strategies for the prevention of visual complications of DR.

METHODS

This was a cross-sectional hospital based study, conducted in the Out- patient Department of Ophthalmology Department, Dhulikhel Hospital, Kathmandu University Hospital from 1st April 2021 to 1st April 2022 after clearance from Institutional review committee (IRC- KUSMS Approval No. 19/2021). All the type II DM patients, of any age and both gender, attending Ophthalmology OPD within the time period of study were included in this study. Patients were enrolled only after obtaining informed written consent from them. Type I DM patients, patients who had already received laser treatment, intra-vitreal injections for the treatment of diabetic retinopathy and patients with hazy media were excluded from the study. Data was collected by interviewing the patient and recording the data in the standard proforma. Then, all the patients underwent visual acuity testing and refraction followed by slit lamp biomicroscopic examination (Haag Streit 900 BQ) for detecting any anterior segment abnormalities. Retinal status was evaluated by slit lamp biomicroscopy using Volk 90 D lens and Heine Indirect ophthalmoscopy using +20D after pupil dilation with tropicamide eye drops 1%. Presence of DR was noted and its grading was done according to International Classification of Diabetic Retinopathy Scale.[13] Fundus photography was performed whenever feasible. HbA1c, Fasting and post-prandial blood glucose level were recorded and evaluated and compared for association with DR and significance.

Data was collected, compiled, and tabulated in a Microsoft Excel sheet. Data was cleaned, and statistical analysis was performed using software SPSS Statistics for Windows, version 25.0 (SPSS Inc., Chicago, Ill., USA). Categorical data was expressed in terms of numbers and percentages, and continuous data was expressed in terms of means and standard deviation. The nature of the data was assessed, and multivariate outliers were checked. Some outliers were detected, which were rechecked and found to represent true data, and since their removal did not change the results significantly, we decided to include them in our final analysis.

Bivariate analysis using t-tests and chi-square tests was used to measure the strength of association between the different variables. An Analysis of Variance (ANOVA) test was used to evaluate the association between the means of different variables. Levene's test confirmed the homogeneity of variances, supporting the use of standard ANOVA. Post-hoc Tukey test was also done to determine the differences between the different groups. We then performed multivariable analysis using a binomial logistic regression model to examine the factors associated with diabetic retinopathy and diabetic macular edema. Only those variables with a p-value of < 0.25 were included in the final parsimonious model. A p-value < 0.05 was considered statistically significant for all types of analysis.

RESULTS

The demographic composition of our study cohort constituted 250 (49.60 %) females and 254 males (50.39%). The mean age of the patients was 55.14 ± 11.37 years. The mean HbA1c, FBS and PPBS were 8.41 ± 2.40, 169.13±86.68 mg/dl and 279.41 ± 133.00 mg/dl respectively (Table 1). Regarding treatment, 426 (84.52%) of the patients were taking oral hypoglycemic agent (OHA) while 14.48% were taking both OHA and insulin. The mean duration of known diabetes among the study population was 5.76 ± 5.93 years. Almost half of the study population had poor glycemic control and deranged FBS and PPBS. In our study,

Table 1. Clinical Characteristics of Enrolled Patients (n= 504)

Features	Mean ± SD
Age (years)	55.13 ± 11.37
Duration of DM (years)	5.76 ± 5.93
FBS (mg%)	169.12 ± 86.68
PPBS (mg%)	279.41 ± 133.00
HB1AC (%)	8.59 ± 4.49

FBS and PPBS were abnormal in 308 (61.11%) patients and 457 (90.67%) patients respectively (Table 2).

Among 504 patients with type II diabetes mellitus, different grades of diabetic retinopathy comprising NPDR, PDR and DME was observed in 168 patients (33.33%). Diabetic retinopathy (NPDR+PDR) was observed in 124 (24.60%) (95% CI: 20.90-28.60) patients. Similarly, diabetic macular edema was observed in 42 (8.33%) (95% CI: 6.07-11.10) patients. Poor control of HbA1c (> 7.6) was seen in 88 (70.96%) cases of diabetic retinopathy and 34 (80.95%) cases of diabetic macular edema. Similarly, uncontrolled fasting and postprandial blood sugar levels were associated with a significant number of cases of diabetic retinopathy and of diabetic macular edema respectively (Table 3).

Our study shows that as the level of HbA1c increases, number of patients with higher grades of diabetic retinopathy and DME increases (Table 3). Patients with good control of HbA1c had no cases of PDR, whereas patients with poor control of HbA1c had 9 (7.25%) cases of PDR. Patients with good control of HbA1c had no cases of DME, but 11 (26.19%) patients with poor control of HbA1c had severe DME. Similarly, patients with uncontrolled FBS and PPBS had increased cases of NPDR, PDR, and DME (Table 3).

Table 2. Glycemic control and blood sugar level among the enrolled diabetic patients.

Glycemic control (Based on HbA1C)	Prevalence
Normal (4.2 – 6.2)	64 (12.69%)
Good (6.3 – 6.8)	87 (17.26%)
Fair (6.9 – 7.6)	109 (21.62%)
Poor (> 7.6)	244 (48.41%)
Total	504 (100%)
Blood sugar level – FBS	
Upto 125 mg/dl	196 (38.88%)
>125 mg/dl (high)	308 (61.11%)
Blood sugar level – PPBS	
Upto 140 mg/ dl	47 (9.32%)
> 140 mg/dl (high)	457 (90.67%)

A statistically significant difference was observed between various grades of diabetic retinopathy and means of FBS, PPBS and HBA1c, respectively (Table 4). The highest HBA1c level i.e. 10.47 ± 9.97% was observed in Moderate NPDR group. In patients with severe DME, highest mean HBA1c (10.45 ± 1.69, p=0.471), highest mean FBS (285.00 ± 146.64, p < .001) and highest mean PPBS (373.41 ± 107.50, p = .035) was observed (Table 4). Comparison of means (ANOVA Test) of HbA1c, FBS and PPBS in each sub-categories for DR and DME showed significant differences of means among the groups except for the means of HbA1c in DME. Tukey's HSD Post-hoc test was done to determine the difference among the groups. Post analysis showed that there was a significant difference among mean of FBS, PPBS and HbA1c among patients with moderate NPDR and patients without diabetic retinopathy, and among patients with severe DME

Table 3. Glycemic control (HBA1c, FBS, PPBS) in patients with Diabetic Retinopathy and Diabetic Macular Edema (N=504)

	Diabetic Retinopathy (N=124)					Diabetic Macular Edema (N=42)			
Glycemic Control	**Mild NPDR**	**Moderate NPDR**	**Severe NPDR**	**PDR**	**Total**	**Mild DME**	**Moderate DME**	**Sever DME**	**Total**
Glycosylated Haemoglobin (HBA1c)									
Normal (4.2 – 6.2)	4	3	0	0	7 (5.64%)	0	1	0	1 (2.38%)
Good (6.3 – 6.8)	6	5	1	0	12 (9.67%)	2	1	0	3 (7.14%)
Fair **(6.9 – 7.6)**	4	10	0	3	17 (13.70%)	1	2	1	4 (9.52%)
Poor (>7.6)	20	56	3	9	88 (70.96%)	12	11	11	34 (80.95%)
Total	34	74	4	12	124 (100%)	15	15	12	42 (100%)
Fasting Blood Sugar (FBS) (mg%)									
Up to 125	2	2	1	1	6 (4.83%)	1	1	0	2 (4.76%)
> 125 (high)	32	72	3	11	118 (95.16%)	14	14	12	40 (95.23%)
Total	34	74	4	12	124 (100%)	15	15	12	42 (100%)
Post Prandial Blood Sugar (PPBS) (mg%)									
Up to 140	5	3	0	1	9 (7.25%)	0	1	0	1 (2.38%)
> 140 (high)	29	71	4	11	115 (92.74%)	15	14	12	41 (97.61%)
Total	34	74	4	12	124 (100%)	15	15	12	42 (100%)

Table 4. **Mean HBA1c, FBS, PPBS based on grades of DR and DME**

Grading of Diabetic Retinopathy	Number of Patients	Percentage	Mean HBA1c	Mean FBS	Mean PPBS
Diabetic Retinopathy					
No DR	**380**	**75.39%**	**8.232 ± 2.49**	**160.17 ± 81.47**	**267.69 ± 134.52**
Mild NPDR	34	6.7%	8.23 ± 1.87	176.79 ± 86.59	281.79 ± 109.32
Moderate NPDR	74	14.68%	10.47 ± 9.97	208.20 ± 103.50	337.81 ± 128.35
Severe NPDR	4	0.79%	9.12 ± 2.75	175.25 ± 61.17	269.50 ± 63.19
PDR	12	2.38%	9.58 ± 2.34	187.91 ± 81.79	287.08 ± 106.17
			p-value = .002**	p-value = <.001**	p-value = .002**
Diabetic Macular Edema					
No DME	**462**	**91.66%**	**8.52 ± 4.64**	**165.00 ± 83.60**	**274.77 ± 135.06**
Mild DME	15	2.91%	8.74 ± 1.94	183.26 ± 69.30	319.33 ± 77.28
Moderate DME	15	2.91%	9.27 ± 2.40	189.06 ± 73.57	307.13 ± 94.82
Severe DME	12	2.38%	10.45 ± 1.69	285.00 ± 146.64	373.41 ± 107.50
			p-value = .014**	p-value = 0.001**	p-value = .033**

*Significant difference found based on post hoc Tukey HSD test.
**p value<0.05 considered significant

Table 5. **Bivariate Regression Analysis between patients clinical characteristics and diabetic retinopathy and diabetic macular edema**

Variables	Diabetic Retinopathy		P value	Diabetic Macular Edema		P value
	Yes	No		Yes	No	
Age	58.46±11.02	54.03±11.29	<0.001*	60.58±10.28	54.54±11.34	<0.001*
Duration of Diabetes	9.60±7.15	4.48±4.85	<0.001*	11.82±8.19	5.09±5.23	<0.001*
Fasting Blood Sugar	195.73±95.78	160.26±81.67	<0.001*	207.36±102.23	164.91±83.87	0.01*
PPBS	313.89±121.44	267.92±134.84	0.001*	325.76±98.10	274.31±135.42	0.01*
HbA1c	9.04±2.19	8.21±2.44	0.001*	9.40±2.06	8.31±2.42	0.03*
Treatment			<0.001*			<0.001*
Oral	91(21.36%)	335(78.64%)		31(62.0%)	395(87.0%)	
Insulin	35(44.87%)	43(55.13%)		19(38.0%)	59(13.0%)	
Gender			0.537			0.591
Male	67(26.38%)	187(73.62%)		27(10.63%)	227(89.37%)	
Female	59(23.60%)	191(76.40%)		23(9.20%)	227(90.80%)	

and patients without DME. No other pairwise comparisons reached statistical significance (Table 4).

Bivariate analysis among blood sugar parameters against development of diabetic retinopathy and diabetic macular edema showed statistically significant association between FBS, PPBS and HbA1c among patients developing diabetic retinopathy, however, only PPBS showed significant association in development of diabetic macular edema (Table 5).

The overall model of logistic regression was statistically significant ($\chi^2(6) = 83.241$, $p < .001$) and fit the data well, as shown by a nonsignificant Hosmer-Lemeshow test ($\chi^2(8) = 10.034$, $p = .263$). The model explained about 22% of the variation in DR (Nagelkerke $R^2 = .225$) and correctly predicted/classified 77% of cases.

Among the predictors, longer duration of diabetes (OR = 1.130, 95% CI [1.086–1.175], $p < .001$) and older age (OR = 1.021, 95% CI [1.000–1.042], $p = .049$) were significantly associated with higher odds of developing DR (Table 6).

DISCUSSION

Chronic hyperglycemia indicated by raised glycosylated hemoglobin value and elevated fasting, post-prandial blood sugar levels, is an important risk factor for the development and progression of diabetic retinopathy. HbA1c is a form of haemoglobin that is chemically linked to a sugar residue. When glucose binds non- enzymatically to a terminal portion of haemoglobin chain, its measurement becomes possible and is directly proportional to blood glucose concentration. HbA1c is the best method for quantification of glycemic control till date. Although much attention has been paid to lowering the HBA1c levels for control of diabetes, lowering the fasting and post- prandial

Table 6. Binary Logistic Regression to assess the association of patient characteristics and Diabetic Retinopathy and Diabetic Macular Edema (n=504)

Variables	Diabetic Retinopathy			Diabetic Macular Edema		
	AOR	95% CI	P value	AOR	95% CI	P value
Age	1.021	1.001-1.042	0.049	1.030	0.993-1.069	0.116
Diabetes Duration	1.130	1.086-1.175*	<0.001	1.052	0.990-1.118	0.100
Treatment						
Oral	1					
Insulin	1.724	0.954-3.116	0.071	1.883	0.789-4.495	0.154
FBS	1.003	0.998-1.008	0.193	1.001	0.995-1.007	0.813
PPBS	1.000	0.997-1.003	0.982	1.000	0.995-1.005	0.962
HbA1C	1.030	0.894-1.186	0.685	1.088	0.864-1.371	0.474

blood glucose levels is equally important for prevention of vascular complications due to diabetes.[14] But compared to FBS and PPBS, the life span of glycosylated hemoglobin is 120 days thus gives us long term glycemic control reports.[15] The mean HBA1c value in our study was 8.59 ± 4.49% which is comparable to mean HBA1c value observed in a study by Chirag et al. and Almutairi et al. as all of these were hospital based studies.[16,17] In contrast to our study, the mean HBA1c value was reported higher as 9.25 ± 1.59 in a study conducted by Nakkella et al. in India.[18] However, lower HBA1c value than our study was reported in a study by Uthman et al in Lahore.[19] These variations may be due to variable study population and other clinical parameters. The mean fasting and postprandial blood sugar levels were 169.12 ± 86.68 and 279.41 ± 113.01 in our study which could not be compared to other studies due to limited literature availability.

Our study shows that as the level of HbA1c increases, severity of DR and DME increases. The milestone randomized clinical trials like Diabetes Control and Complications Trial (DCCT) and the U.K. Prospective Diabetes Study (UKPDS) also indicated that intensive glycemic control delays the onset and progression of diabetic retinopathy.[3,5] In Barbados eye study, every 1% increase in HbA1c from baseline was associated with a > 2 fold risk of diabetic retinopathy and up to four years follow up revealed the linear relationship of HbA1c level with development and progression of DR.[20]

Studies conducted by Nakkella et al., Kant et al., Prasad et al. and Lokesh et al. in India also concluded that increased levels of HbA1c was observed in severe grades of DR with clinically significant macular edema (CSME).[18,21-23] Studies conducted in Iran and Japan also revealed that higher the levels of fasting plasma glucose and HbA1c, higher is the prevalence of diabetic retinopathy.[24,25] In concordance to our study, studies conducted by Singh et al. and Bukke et al. revealed presence of positive correlation between mean HbA1c and grades of diabetic retinopathy.[16,26] Studies conducted by Uthman et al. in Lahore and Hoque et al. in Bangladesh also concluded that increasing HbA1c is directly related to progression of diabetic retinopathy.[19,27] Similarly study conducted by Cheng et al. in the U.S. population also revealed that HbA1c ≥ 5.5% and FPG ≥ 5.8 mmol/l are associated with increasing levels of retinopathy.[28] Several other studies also reported that when FBS exceeded 7.03 mmol/L and HbA1c > 6.4%, the prevalence of DR increased sharply.[16,29]

However in a study conducted by Almutairi et al. in Saudi Arabia, there was a significant association between the development of DR and HbA1c Levels but no statistically significant relationship between HbA1c and the severity of DR.[17]

Our study revealed that controlled FBS and PPBS are equally important to achieve optimal glycemic control but PPBS has significant association with HbA1c and is a better predictor of overall glycemic control compared to FBS, which is similar to other studies.[30,31] Few studies also reported that higher fasting and post-prandial blood sugar levels are major risk factors for developing diabetic retinopathy.[14,32,33] But the association of FBS, PPBS with DR has not been extensively explored as much as HbA1c thus need further studies to analyze the association.

Thus, optimal glycemic control is by far the most important factor in the effective management of diabetic retinopathy as implicated by our study and both the landmark trials like DCCT and UKPDS trials. Intensive glycemic control is associated with a reduced risk of a new onset of retinopathy, reduced progression of retinopathy from NPDR to PDR, decreased incidence of DME, reduced need for panretinal photocoagulation, anti VEGFs and surgery. Vigorous monitoring of blood sugar levels and HbA1c with modification in treatment regimen accordingly decreases the morbidity, macro and microvascular complications including diabetic retinopathy and other morbidities.

There were few limitations in this study. First no control group was included and blood glucose levels were based only on single measurement. Due to cross-sectional design of the study, progression of diabetic retinopathy could not be monitored. Patients with known diabetes and under anti-diabetic medications were included in this study which

may have caused bias in the occurrence of hyperglycemia and retinopathy in the patients.

CONCLUSION

Optimal glycemic control is by far the most important factor in the effective management of diabetic retinopathy as implicated by our study. There is a strong association between glycemic control and development of diabetic retinopathy.

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