Original Article

Evaluation of HbA1c Level and Other Risk Factors in Diabetic Retinopathy: A Study of Type 2 Diabetic Patients Attending in a Tertiary Level Hospital

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Abstract

Background: *Retinopathy is the leading cause of blindness in persons with diabetes. Strict monitoring and maintenance of normal blood glucose specially HbA1c and prevention of different risk factors can prevent and delay the diabetic retinopathy. The purpose of the study was to explore the factors influencing or related to the development of the diabetic retinopathy with spcial concern to the HbA1c levels.* ***Materials and Methods:*** *We studied 400 type 2 diabetic patients in this cross-sectional study which was conducted in the out-patient department of BIRDEM hospital, Bangladesh. The randomly selected patients were evaluated for the presence of retinopathy through the review of their registered diabetic guide book. We included sociodemographic information, blood pressure, anthropometry (height, weight, BMI) and lipid profile of the patients. Glycaemic status was assessed by HbA1c (HbA1c was categorized into 3 groups) and plasma glucose levels. We used Student's t-test, Chi-square test and logistic regression analysis to determine and quantify the association of diabetic retinopathy with various risk factors specially HbA1c.* ***Results:*** *400 type 2 diabetic patients (male 166 and female 234) were studied. The prevalence of retinopathy was 12.3%; male 12.7%, female 12.0%. Increasing HbA1c categories above 7.0% were significantly associated with increased prevalence of retinopathy (4.2 vs 12.3 vs 18.1%; χ^2 = 12.529, p < .01). Logistic regression models of univariate analysis showed that the risk of retinopathy at HbA1c categories >7.0% was (OR = 3.22; 95% CI: 1.12-9.25) and the risk was strongly increased at the HbA1c categories ≥8% (OR = 5.07; 95% CI: 1.90-13.50). Advanced age (OR = 2.92; 95% CI: 1.44-5.91), longer duration of diabetes (OR = 3.08; 95% CI: 1.49-6.37), presence of hypertension (OR = 2.42; 95% CI: 1.14-5.16), FBG (OR = 1.139; 95% CI: 1.036-1.251), blood glucose 2 hours ABF (OR = 1.124; 95% CI: 1.046-1.207) and SBP (OR = 1.033; 95% CI: 1.011-1.056) had significant association with retinopathy.* ***Conclusions:*** *HbA1c categories >7.0% is an important risk factor for the development of retinopathy. Poor glycaemic control, advanced age, longer duration of diabetes, hypertension are other significant risk factors of diabetic retinopathy.*

Key words: *Retinopathy, HbA1c, Risk factors, Type 2 diabetes.*

Introduction

Diabetic retinopathy is one of the most prevalent microvascular complications of diabetes. It is the leading cause of blindness globally. It is responsible for approximately 10000 new cases of blindness every year in the United States alone[1]. Retinopathy may begin to develop as early as 7 years before the diagnosis of diabetes in patients with type 2 diabetes.

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Some degree of retinopathy is evident after 15-20 years in nearly all type 1 diabetics and in more than 60% of type 2 diabetics[2]. Several studies have observed that advanced age, longer duration of diabetes, poor glycaemic control, hypertension, dyslipidaemia, physical inactivity, microalbuminuria etc. are the contributory risk factors of retinopathy[2-5]. Long term clinical studies strongly suggest that hyperglycaemia or closely associated factors of poor glycaemic control, like HbA1c is of major importance in both the initiation and progression of retinopathy[6]. Different randomized controlled trials and observational studies have shown that glycated hemoglobin or HbA1c is a good predictor of microvascular complications including retinopathy in patients with or without diabetes[2,6-9]. It indicates that HbA1c may be used as a useful marker for retinopathy along with other risk factors.

In a recent trial (DETECT-2, 45,000 participants), based on logistic regression, HbA1c threshold for diabetes-specific retinopathy was observed in the range of 6.3-6.7%[10]. One study demonstrated that the risk of retinopathy starts to increase as HbA1c rises above 6.6%-6.7%[11]. Another study by Sabanayagam et al showed that, increasing HbA1c categories had a higher prevalence of any retinopathy, mild retinopathy and moderate retinopathy in a dose-dependent manner (p trend <0.0001 for any retinopathy, mild retinopathy and moderate retinopathy). In the multivariable models, HbA1c categories above 7.0% were significantly associated with increased prevalence of retinopathy compared with the lowest category[12]. In Malay study the thresholds of HbA1c were 6.6% for any retinopathy and 7.0% for moderate or severe retinopathy[10]. In a South Korean study the cutoff were 6.6% and 6.9% respectively[13]. According to review by Kowall and Rathmann, HbA1c cutoffs derived from predominantly cross-sectional studies on retinopathy differ widely from 5.2-7.8%, and among other reasons, this is due to the heterogencity of statistical methods and in the definition of retinopathy[14]. In Bangladesh there are a very few clinical studies on relation of HbA1c and other risk factors with retinopathy[15]. Therefore, we attempted to do a clinical study in this regard. Our aim was to gain new insights into how different risk factors specially HbA1c affect and reflect the risk of retinopathy among patients with type 2 diabetes.

Materials and Methods

We carried out a cross-sectional study in the outpatient department (OPD) of BIRDEM hospital, Dhaka, Bangladesh from January 2014 to December 2014. A total of 400 type 2 diabetic patients of both gender and age group 30-60 years were included as study participants. The average duration of type 2 diabetes for the population was approximately 6.41 years ranging from 2 to 10 years. Patients with other chronic illnesses (like chronic hepatic diseases, chronic arthritis etc.) those may interfere with the blood glucose levels, pregnant diabetic cases or gestational diabetes, type 1 diabetics and patients of hemoglobinopathies were excluded from the study. The information of the patients were availed from their 'diabetic guide book'. This registered medical record book contained all records of baseline information and recorded necessary advice to diabetes management for subsequent follow-up visit.

In this study we collected data about sociodemographic information (age, sex, family history of diabetes, geographical location, socioeconomic factor, educational history, occupational history), lifestyle characteristics (physical activity, smoking history etc.), blood pressure and anthropometry (height, weight, calculated BMI) of the participants. The age of onset and duration of diabetes were also recorded. The selected patients were evaluated for the presence of retinopathy through the review of physicians' notes in the patients' medical report which were recorded in their diabetic guide book. We could not divide the total retinopathy patients according to their classification as the number of retinopathy patients in different groups (according to their classification) was small. The glycaemic status of the participants were assessed by HbA1c, fasting plasma glucose level and 2 hours after breakfast blood glucose level. In this study we categorized the study participants into 3 groups by 3 HbA1c categories. These were good control group (HbA1c <7.0%), average control group (HbA1c 7-7.9%) and poor control group (HbA1c $\geq$ 8.0%). We compared the participants in these 3 HbA1c categories. HbA1c was measured by BIO-RAD variant which was modified HPLC method. Serum creatinine levels and fasting lipid profile were also measured.

Statistical analysis

The prevalence rate of retinopathy among type 2 diabetes was determined by simple percentages. For comparison of different variables among the groups we used Chi-square test for categorical data and Student's t-test for quantitative data. Univariate and multivariate logistic regression analyses were performed to identify factors associated with retinopathy and adjusted for potential confounding factors. Odds ratio (OR) with 95% confidence interval (CI) were provided. All -

statistical tests were considered significant at a level of $p < 0.05$. SPSS software, version 21 was used for the statistical analysis.

Results

Among the study subjects 41.5% (166) were male and 58.5% (234) were female. The mean age of the study participants during study time was 50.05 (±7.528) years. The range of duration of diabetes was 2-10 years and mean duration was 6.41 (±3.06) years. The overall prevalence of retinopathy was 12.3%; male 12.7%, female 12.0%. Among the study participants the mean HbA1c was 7.99% (±1.80). Table I shows that the prevalence of retinopathy was significantly higher in age group ≥50 years than <50 years (16.7 vs 6.4%; χ^2 = 9.622, p =.002). Presence of hypertension was significantly higher in retinopathy (15.0 vs 6.8%; χ^2 = 5.573, p = .018).

Table I: Association of different sociodemographic characteristics of the study participants with retinopathy

Variables	Total subjects (n=400)	Retinopathy no of cases (%)	*p* value
Age group (years)			
<50	172	11 (6.4)	**.002**
≥ 50	228	38 (16.7)	
Duration of diabetes (years)			
2-5	165	10 (6.1)	**.002**
6-10	235	39 (16.6)	
Gender			
Male	166	21 (12.7)	.837
Female	234	28 (12.0)	
Residence			
Urban	291	33 (11.3)	.365
Not urban	109	16 (14.7)	
Educational status			
Schooling	310	38 (12.3)	.993
No schooling	90	11 (12.2)	
Exercise done by patients			
Yes	195	20 (10.3)	.236
No	205	29 (14.1)	
Family history of diabetes			
Yes	261	37 (14.2)	.107
No	139	12 (8.6)	
Presence of hypertension			
Yes	267	40 (15.0)	**.018**
No	133	9 (6.8)	

On univariate logistic regression analysis we observed that advanced age (OR = 2.92; 95% CI: 1.44-5.91), longer duration of diabetes (OR = 3.08; 95% CI: 1.49-6.37), presence of hypertension (OR = 2.42; 95% CI:1.14-5.16) had significant association with retinopathy. When we compared male and female with retinopathy we could not find any significant difference. Residence, educational status, family history of diabetes and lacking of physical exercise also did not show any significant association with retinopathy (Table I and II).

We observed that patients with retinopathy had a significantly higher mean age than the rest of the study sample (53.94 ± 5.336 vs 49.51 ± 7.635, p = .000).

Table II Univariate logistic regression analysis showing different variables associated with retinopathy

Variables	Odds Ratio (95% CI)	*P*-value
HbA_{1c} (%)		
<7	1.0	
7-7.9	3.22 (1.12-9.25)	**.03**
≥8	5.07 (1.90-13.50)	**.001**
Age (years)		
<50	1.0	
≥50	2.92 (1.44-5.91)	**.003**
Gender		
Female	1.0	
Male	1.066 (0.58-1.95)	.837
Duration of diabetes (years)		
2 -5	1.0	
>6-10	3.08 (1.49-6.37)	**.002**
Exercise done by patients		
Yes	1.0	
No	1.44 (0.78-2.64)	.237
Presence of hypertension		
No	1.0	
Yes	2.42 (1.14-5.16)	**.021**
FBG	1.139 (1.036-1.251)	**.007**
2hours ABF	1.124 (1.046-1.207)	**.001**
SBP	1.033 (1.011-1.056)	**.003**
DBP	1.024 (.982-1.068)	.271

Duration of diabetes also showed significant difference between the patients with and without retinopathy (8.02 ± 2.618 vs 6.19 ± 3.062, p = .000). HbA1c (8.937 ± 1.947 vs 7.864 ± 1.747, p = .000), fasting blood glucose (10.253 ± 2.449 vs 9.069 ± 2.843, p = .006), blood glucose 2 hours after breakfast (14.838 ± 3.667 vs 12.833 ± 4.023, p = .001) and systolic blood pressure (132.65 ± 11.641 vs 126.77 ± 13.017, p = .003) were-

Table III Clinical variables related to retinopathy

Variables	Total participants (n=400)		p value
	With Retinopathy (n=49) Mean ± SD	Without Retinopathy (n=351) Mean ± SD	
Age (years)	53.94 ± 5.33	49.51 ± 7.64	**.000**
Duration of diabetes (years)	8.02 ± 2.6 2	6.19 ± 3.06	**.000**
BMI (kg/m2)	24.39 ± 3.0 9	24.98 ± 3.56	.270
SBP (mm of Hg)	132.65 ± 11.64	126.77 ± 13.02	**.003**
DBP (mm of Hg)	82.14 ± 6.99	80.98 ± 6.89	.271
HbA_{1c} (%)	8.937 ± 1.95	7.864 ± 1.7 5	**.000**
FBG (mmol/L)	10.253 ± 2.45	9.069 ± 2.84	**.006**
2 hours ABF (mmol/L)	14.838 ± 3.6 7	12.833 ± 4.02	**.001**
Total cholesterol (mg/dl)	196.92 ± 46.63	187.68 ± 43.9 4	.172
Triglyceride (mg/dl)	199.30 ± 110.67	211.48 ± 132.780	.540
LDL cholesterol (mg/dl)	120.35 ± 41.05	111.09 ± 39.670	.141
HDL cholesterol (mg/dl)	40.20 ± 10.35	38.19 ± 7.94	.125

* FBG - Fasting blood glucose, 2 hours ABF - blood glucose 2 hours after breakfast, SBP- Systolic blood pressure, DBP- Diastolic blood pressure.

significantly higher in patients with retinopathy. BMI, diastolic blood pressure, and lipid profile did not show any significant difference (Table III). On univariate logistic regression analysis we found that FBG (OR = 1.139; 95% CI: 1.036-1.251), blood glucose 2 hours ABF (OR = 1.124; 95% CI: 1.046-1.207) and SBP (OR = 1.033; 95% CI: 1.011-1.056) had significant association with retinopathy (Table II).

The details of relationship of retinopathy with HbA1c is shown in Table II, IV and Figure 1. We found that increasing HbA1c categories had a higher prevalence of retinopathy compared with the lower category. The increasing HbA1c categories above 7.0% were significantly associated (4.2 vs 12.3 vs 18.1%; χ^2 = 12.529, p = .002) with increased prevalence of retinopathy. We used the univariate logistic regression analysis to quantify the individual effect of HbA1c with retinopathy as dependent variable. HbA1c category 7-7.9% found to be a significant risk factor for developing retinopathy (OR = 3.22; 95% CI: 1.12-9.25) and the risk increases more at HbA1c category ≥ 8% (OR = 5.07; 95% CI: 1.90-13.50).

Table IV Relationship between retinopathy and HbA1c categories.

HbA 1c categories (%)	With retinopathy	Without retinopathy	Total	χ^2	p value
<7	5 (4.2%)	115 (95.8%)	120		
7-7.9	14 (12.3%)	100 (87.7%)	114	12.529	**.002**
≥8	30 (18.1%)	136 (81.9%)	166		
Total	49 (12.3%)	351 (87.8%)	400		

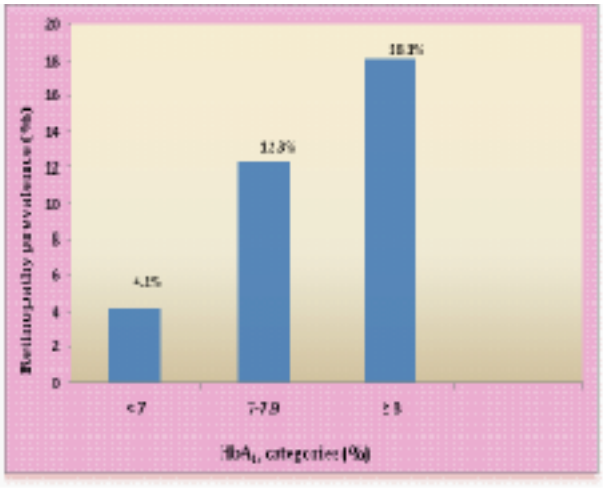

Figure 1 Relationship between retinopathy and HbA1c

On multivariate analysis after adjusting potential confounding factors (advanced age, longer duration of diabetes, gender, hypertension) we found that HbA1c category ≥ 8% (OR = 3.59; 95% CI: 1.299-9.931), older age (OR = 1.084; 95% CI: 1.026-1.145) and higher duration of DM (OR = 1.152; 95% CI: 1.018-1.304) are important risk factors for retinopathy (Table V).

Table V Multivariate analysis of risk factors for retinopathy

Variables	Odds Ratio (95% CI)	P-value
HbA 1c (%)		
<7	1.0	
7-7.9	2.060 (.691 -6.141)	.195
≥8	3.592 (1.299 -9.931)	**.014**
Age	1.084 (1.026 -1.145)	**.004**
Gender		
Female	1.0	
Male	1.024 (.539-1.947)	.942
Duration of diabetes	1.152 (1.018-1.304)	**.025**
Presence of hypertension		
No	1.0	
Yes	1.737 (.788 -3.826)	.171

Discussion

In our study the prevalence of retinopathy was 12.3% with male 12.7% and female 12.0%. In a study conducted in India showed the prevalence of retinopathy was 17%[3]. Knuiman et al reported the prevalence of retinopathy as 28% in a study from Perth (Western Australia)[16]. These differences in prevalence of retinopathy in different countries may be due to different diagnostic criterias of retinopathy. Several studies indicated that HbA1c may show a glycaemic threshold with retinopathy, suggesting it may additionally be useful biomarker to identify individuals at risk for retinopathy[12,17-18].

In our study we observed that increasing HbA1c categories above 7.0% were significantly associated with increased prevalence of retinopathy. Our results were consistent with Sabanayagam et al who reported that increasing HbA1c categories had a higher prevalence of any retinopathy, mild retinopathy and moderate retinopathy[11]. Another study also found the similar association of HbA1c with retinopathy[4]. Zoungas et al observed that the apparent threshold of HbA1c level for different microvascular complications including retinopathy was 6.5%. They also revealed that above thresholds, a higher level of HbA1c was significantly associated with higher risk of retinopathy events in a log-linear manner. Below these thresholds, there was no significant relationship between mean

HbA1c level and risks[17]. In our study there were relatively few retinopathy events observed at HbA1c levels less than 7.0% so we could not properly evaluate the relation of retinopathy with HbA1c levels below 7.0%. This may be due to the limited sample size.

We observed increased prevalence of retinopathy with advanced age and longer duration of diabetes. Similar strong associations were also found in some other studies[3-4,15,19]. Our observation of association of retinopathy with hypertension has also been recorded by many workers previously[19-20]. We found that an increased mean HbA1c was significantly associated with retinopathy. Higher blood glucose levels in fasting and 2 hours after breakfast both found to be major risk factors for retinopathy. These findings were consistent with other studies[3-4]. We also found that higher systolic blood pressure was an important risk factor for retinopathy; however diastolic blood pressure had no significant contribution to retinopathy. The strong relation of higher systolic blood pressure and retinopathy was also observed by Agrawal et al[4].

Conclusions

Our data suggest that higher HbA1c level >7% is significant risk factor of retinopathy and the risk increases markedly at HbA1c levels ≥ 8%. Advanced age, longer duration of diabetes, hypertension and poor glycaemic control are another important predictors of retinopathy. These findings highlight the need for primary care physicians to be aware of the possible presence of these risk factors of retinopathy among their diabetic patients, so that the occurrence and worsening of retinopathy among type 2 diabetic patients could be prevented or atleast delayed.

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