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Indian Journal of Clinical and Experimental Ophthalmology

Journal homepage: www.ijceo.org

Original Research Article

Association of HbA1c levels with diabetic retinopathy

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ARTICLE INFO

Article history:
Received 03-12-2020
Accepted 22-12-2020
Available online 30-06-2021

Keywords:
Glycosylated Haemoglobin
HbA1c
Diabetic Retinopathy
Hypertension
Fasting blood glucose

ABSTRACT

Purpose: To study the association of HbA1C levels with diabetic retinopathy.
Materials and Methods: A total of 330 diagnosed diabetic subjects of all age groups and genders participated in the study. They were grouped according to presence or absence of diabetic retinopathy. All patients HbA1C levels along with fasting blood glucose levels was obtained. Observations were made to find the association between HbA1C levels and diabetic retinopathy.
Results: Mean HbA1c level among diabetic retinopathy subjects (9.50) was higher than subjects without retinopathy (8.49). The difference was found to be statistically significant ($p < 0.05$). With high HbA1c levels high mean fasting blood glucose levels were associated (R value: 0.5856). This is a moderate positive correlation.
Conclusion: As glycosylated haemoglobin (HbA1c) levels increases prevalence of diabetic retinopathy also increases and there is a strong relationship between HbA1c levels and diabetic retinopathy.

1. Introduction

According to WHO, Diabetes Mellitus refers to a group of metabolic disorders that share the phenotype of hyperglycemia and is defined as when a person has more > 2 readings of fasting plasma glucose of 126 mg/dl or 2-hour post-prandial glucose level >200 mg/dl or glycosylated haemoglobin (HbA1c) > 6.5%. This prolonged hyperglycemia is result from the defect in insulin secretion, insulin action or both.[1] DM is classified into 2 categories: Type 1 is an Insulin dependent diabetes mellitus (IDDM) accounting for about 10% of DM cases and Type 2 which is non-insulin dependent diabetes mellitus (NIDDM) accounting for about 90% of cases.

Data from the 2015 International Diabetes Federation Atlas report that DM affects 415 million people globally.[2] With uncontrolled population increasing daily, more caloric consumption and with advancement in technology people shifting towards sedentary lifestyle, this number is projected to reach 640 million by 2040, making diabetes as one of the largest global health issues of 21st century.[2]

India is considered as world capital of Diabetes. According to WHO, India has about 70 million people living with diabetes in 2015, increasing to 98 million by 2030.[3]

Diabetic retinopathy is among the most common causes of legal blindness affecting the age group of 20-74 years of age and is a frequent microvascular complications of DM.[4] The prevalence of DR is considerably higher in type 1 than in type 2 DM, seen in all patients of type 1 & 70% of type 2 DM after 15 years of DM.[5,6]

Patients suffering from retinopathy are initially asymptomatic but gradually experience floaters, distortion and blurred vision which may later progress to irreversible changes. The relative risk of blindness in diabetes patients is approximately 5 times the risk of those without diabetes after adjusting for potential confounders.[7]

Glycosylated haemoglobin is non enzymatic addition of a sugar residue to haemoglobin. When glucose is bound

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https://doi.org/10.18231/j.ijceo.2021.067

non-enzymatically to a terminal portion of Hb chain, its quantization becomes possible. This measurement is directly proportional to blood glucose concentration.[8] As life span of RBCs is 120 days, this test, with allowances for the dynamics of RBCs production & disposal, indicate mean blood glucose over a 2- 3month period. At present, the consensus on best method for measuring glycosylated haemoglobin is to use a fractionated value of HbA1c. The normal value of HbA1c is < 6.9% of total haemoglobin.

DR is one of the most common causes of blindness, therefore there should be an effort for early diagnosis and treatment of DR. Poor glucose control is a risk factor and glycosylated haemoglobin indicates long term blood glucose concentration. This study has been done to establish an association between HbA1c levels with diabetic retinopathy so that progression of diabetic retinopathy can be predicted and early intervention can be instituted.

2. Materials and Methods

A hospital based observational analytical cross sectional study was conducted in a tertiary hospital and research centre in Pimpri Pune from the period of September 2018 to August 2020 after clearance from the ethics committee of the institute. Well informed consent was procured from all the subjects. The study was conducted in a total of 330 subjects in the all age group including both the sexes. The inclusion criteria was subjects with diagnosed diabetes mellitus. Exclusion criteria was patients with high myopes, patients with vitreo retinal degenerations and dystrophies, patients in hypertensive emergencies, or with active infections or patients having ocular diseases like hazy media and uveitis and patients with retinal diseases like retinal vascular oclusins or retinitis pigmentosa.

Participant Information Sheet(PIS) regarding details of study were prepared in English, Marathi and Hindi languages. PIS was given to the participants and they were explained about the type and purpose of study according to the language best understood. After due consent only they were enrolled in the study. Patients' rights for participation in the study were safeguarded. Participation in the study was voluntary. Participants were free to withdraw from the study at any point without giving any reason and without any loss to medical care.

Thorough ophthalmic examination of both the eyes was done. Visual acuity was assessed-distant vision by Snellen 's chart and near vision by Jaeger's chart. Auto Refractometry and BCVA (Best Corrected Visual Acuity) was done followed by slit lamp biomicroscopic examination of anterior segment. Retinal status was evaluated by indirect ophthalmoscopy and +20D after dilatation with Tropicamide plus eye drops. Diabetic retinopathy was graded according to Early Treatment Diabetic Retinopathy (ETDRS) criteria. All patients HbA1c levels were evaluated and were compared for association and significance.

Data was collected, compiled and tabulated in Microsoft Excel sheet. The statistical analysis will be performed using software like Primer or SPSS 20. Quantitative data was analyzed in percentage and proportion. Qualitative data was analyzed with appropriate test of significance like Chi square test and t- student test to compare discrete variables. Confidence interval with P-value of <0.05 as a level of significance was applied.

3. Results

Out of the 330 subjects, 69.09% (228) subjects were in the age group 51-65 years, 16.36% (54) were between 36 and 50, 13.33% (44) were in 66-80 years, 0.91% (3) in 21-35 years and 0.3% (1) was above 80 years. Of the 232 subjects with DR, 71.55% (166) were in the age range 51-65 years, 15.52% (36) in 66-80 years, 12.07% (28) in 36-50 years, 0.43% (1) in 21-35 years and 0.43% (1) above 80 years. Most of the patients (69.1%) were in the 51-65 age range.

Out of 330 subjects 57.88% (191) were males and 42.12% (139) were females. Of the 232 patients with DR, 60.78% (141) were males and 39.22% (91) were female.

Of the 330 patients enrolled, 94.24% (311) had T2DM while 5.76% (19) had T1DM. In the patients diagnosed with DR, 93.97% (218) had T2DM while 6.03% (14) had T1DM. Of the 19 patients with T1DM, 74% (14) developed DR while 70% (218) of T2DM patients developed DR.

Average duration of diabetes was 9.46±4.97 years in the study population and 10.39±5.01 in the subjects with DR.

Of 330 subjects enrolled, 30% (99) had hypertension, 8.18% (27) had hyperlipidemia, 5.45% (18) had IHD, 0.91% (3) had CKD, 0.61% (2) had asthma and 0.3% (1) each of acromegaly, HbsAg+ and hypothyroidism. Of the 232 DR patients, 33.19% (77) had hypertension, 14.22% (33) had hyperlipidemia, 5.17% (12) had IHD, 1.29% (3) had CKD, 0.86% (2) has asthma and 0.43% (1) had hypothyroidism. Hypertension is the most common co-morbidity found associated in subjects with DR.

Of 330 subjects, there was no PDR/ NPDR in 32.73% (108) of the patients while 9.7% (32) patients had mild NPDR, 31.21% (103) had moderate, 2.73% (9) had severe and 1.82% (6) had very severe NPDR. 21.82% (72) had PDR in the right eye.

While in Left eye of 33.33% (110) patients was normal with no disease whereas 9.39% (31) had mild NPDR, 30% (99) had moderate NPDR, 3.94% (13) had severe NPDR and 2.12% (7) had very severe NPDR. 21.21% (70) patients had PDR.

Mean HbA1c level in the study was 8.6 mg/dl with a SD of +2.13.

In our study, fasting blood sugar level was <100 in 16 patients (7 eyes had NPDR), 101- 150 in 143 (131 eyes had NPDR), 151-200 in 88 (118 eyes had NPDR and 32 had PDR), 201-250 in 34 (23 eyes had NPDR and 41 had PDR), 251-300 in 30 (15 eyes had NPDR and 41 had PDR)

and >300 in 19 patients (6 eyes had NPDR and 28 eyes had PDR).

In our study, mean fasting blood sugar level was 174.63 with a SD of +65.72 mg/dl.

Patients with less than 6 HbA1c level have 138mg/dl as mean fasting blood glucose level. Between 6-7 HbA1c level mean fasting blood glucose was 135.85 mg/dl, between 7-8 have 151.45mg/dl while between 8-9 patients have 177.55 mg/dl as mean blood glucose level. While patients with more than 9 HbA1c level have 223.87 mg/dl as mean blood glucose level.

Table 1: Age distribution

Age Distribution	No. of Patients (%)	No. of Patients with DR (%)
21 to 35	3 (0.91)	1 (0.43)
36 to 50	54 (16.36)	28 (12.07)
51 to 65	228 (69.09)	166 (71.55)
66 to 80	44 (13.33)	36 (15.52)
81 and above	1(0.30)	1 (0.43)

Table 2: Gender distribution

Gender Distribution	No. of Patients (%)	No. of Patients with DR
Female	139 (42.12)	91 (39.22)
Male	191 (57.88)	141 (60.78)

Table 3: Type of diabetes mellitus

Type of Diabetes Mellitus	No. of Patients (%)	No. of Patients with DR (%)
Type 1	19 (5.76)	14 (6.03)
Type 2	311 (94.24)	218 (93.97

Table 4: Duration of diabetes mellitus (years)

Duration of Diabetes Mellitus (years)	
Mean	9.46
Std Dev	4.97

4. Discussion

Out of the 330 subjects enrolled, 70.3% (232) had diabetic retinopathy. Lokesh S et al. reported prevalence of DR as 64%, in Blue mountain study[9] it was 29% while the prevalence rate was 50.3% in Winconsin epidemiologic study.[10] Chennai urban Rural Epidemiological study (CURES) showed an overall prevalence of diabetic retinopathy of 17.6%.[11] In a study conducted by Khalid M et al[12] in Saudi Arabia prevalence of DR was 35.8%, two studies conducted in USA by reported a prevalence of 28.2% and 28.5%.[13,14] In a study conducted in UK DR.[15] prevalence of DR was 30.1%.

In our study, of the 330 patients, 69.09% (228) patients were in the age group 51-65. Of the 23 patients with DR, 71.55% (166) were in the age range 51-65 years, 15.52% (36) in 66-80 years, 12.07% (28) in 36-50 years, 0.43% (1) in 21-35 years and 0.43% (1) above 80 years. Most of the patients (69.1%) were in the 51-65 age range. In a study by Lokesh S et al,[16] majority of the patients (38%) were in the age range 61-70 years. Similar findings were reported by Khalid M et al,[12] Pragati Garg,[17] Zhang R,[18] Long M[19] where majority of the patients were above the age of 50 years.

In our study, 57.88% (191) were males and 42.12% (139) were females. Of the 232 patients with DR, 60.78% (141) were males and 39.22% (91) were female. Male to female ratio was 1.37:1 in the entire study group and it was 1.55:1 among patients with DR. Literature reported mild preponderance of males, as seen in studies by Lokesh S et al. (68%) [85], Khalid MA (61.4%). However, in studies by Pragati G et al. (46.85%) and Long M et al. (47.2%) [88] number of female patients was slightly greater than the males.

Of the 330 patients enrolled, 94.24% (311) had T2DM while 5.76% (19) had T1DM. In the patients diagnosed with DR, 93.97% (218) had T2DM while 6.03% (14) had T1DM. Of the 19 patients with T1DM, 74% (14) developed DR while 70% (218) of T2DM patients developed DR. In a study conducted by Thomas RL et al,[15] prevalence of any DR in those with Type 1 diabetes was 56.0%, and in Type 2 diabetes was 30.3%. Matuszewski W et al[20] reported that the prevalence of any DR in T1DM was 32.58% and 23.4% in T2DM in north-east Poland. In a nine-year follow-up study conducted by Romero-Aroca P et al,[21] the incidence of any DR was 47.26% with annual incidence 15.16% in T1DM, and 26.49% with annual incidence 8.13% in Type 2 Diabetes Mellitus. In a study conducted in Scotland[22] data revealed a higher cumulative incidence of DR in patients with T1DM (21.7%) than in those with T2DM (13.3%).

Average duration of diabetes was 9.46 ± 4.97 years in the study population and 10.39 ± 5.01 in the patients with DR. In the study conducted by Lokesh S et al,[16] average duration of diabetes mellitus was 9.8 ± 5.34 years. Long M et al. reported that severe NPDR/proliferative retinopathy had the longest duration of diabetes followed by those with mild NPDR (14.4 years) then subjects with no retinopathy (7.5 years). Karadeniz Z et al[23] reported that the presence and the severity of DR was increasing as the duration of DM increases. In a study conducted by Ramanathan RS,[24] 40% patients of DR had duration between 10-15 years, 55% patients had a duration of >15 years. Melo, L.G.N et al[25] also reported that longer duration of DM is a risk factor for development of DR.

Of 320 patients enrolled, 30% (99) had hypertension, Hypertension is the most common co-morbidity in patients with DR. In Lokesh S et al. study,[16] 54% of patients

Table 5: Associated diseases

Associated diseases	No. of Patients (%)	Percentage of Patients	No. of patients with DR (%)	Percentage of patients with DR
Asthma	2 (0.61)	0.61%	2(0.86)	0.86%
IHD	18(5.45)	5.45%	12(5.17)	5.17%
Hypertension	99(30)	30.00%	77(33.19)	33.19%
Hyperlipidemia	27(8.18)	8.18%	33(14.22)	14.22%
CKD	3(0.91)	0.91%	3(1.29)	1.29%
Acromegaly	1(0.30)	0.30%	0(0)	0.00%
HbsAg+	1(0.30)	0.30%	0(0)	0.00%
Hypothyroidism	1(0.30)	0.30%	1(0.43)	0.43%

Table 6: ETDRS classification and mean HbA1c - right eye

ETDRS Classification- RT eye	No. of Patients	Percentage of Patients	Mean HbA1c	Mean Duration of diabetes in years
No Disease	108	32.73%	8.55	7.19
Mild NPDR	32	9.70%	8.11	8
Moderate NPDR	103	31.21%	8.2	9.61
Severe NPDR	9	2.73%	8.95	11.44
Very Severe NPDR	6	1.82%	7.63	11.33
PDR	72	21.82%	9.49	12.05
Correlation	The value of R is 0.3433, co-efficient of determination:0.1179 suggests a positive correlation between mean GHL and duration of diabetes and grade of diabetic retinopathy.			

Table 7: ETDRS classification & HbA1c - Left Eye

ETDRS Classification- LT eye	No. of Patients	Percentage of Patients	Mean HbA1c	Mean Duration of diabetes in years
No Disease	110	33.33%	8.44	7.08
Mild NPDR	31	9.39%	8.05	8.32
Moderate NPDR	99	30.00%	8.29	9.76
Severe NPDR	13	3.94%	8.99	10.69
Very Severe NPDR	7	2.12%	8.03	12.83
PDR	70	21.21%	9.52	12.32
Correlation	The value of R is 0.3489, Co-efficient of determination:0.1217 suggests a positive correlation between mean GHL and duration of diabetes and grade of diabetic retinopathy.			

Table 8: Glycosylated hemoglobin level

Glycosylated Hemoglobin Level	
Mean	8.60
Std Dev	2.13

Table 9: BSL-F(mg/dl)2

BSL-F(mg/dl)2	No. of Patients	No. of Eyes with NPDR	No. of Eyes with PDR
<100	16	7	0
101-150	143	131	0
151-200	88	118	32
201-250	34	23	41
251-300	30	15	41
>300	19	6	28

Table 10: HbA1c

HbA1c	No. of Patients	No. of Eyes with NPDR	No. of Eyes with PDR
<6	12	12	3
6.0 - 7.0	62	58	8
7.1 - 8.0	84	87	21
8.1 - 9.0	81	87	39
>9	91	55	71

Table 11: BSL-F

BSL-F (mg/dl)	
Mean	174.63
Std Dev	65.72

Table 12: Correlation between HbA1c and mean BSL-F

HbA1c	**Mean BSL-F**
<6	138.41
6.0 - 7.0	135.85
7.1 - 8.0	151.45
8.1 - 9.0	177.55
>9	223.87

had coexisting hypertension. Two studies conducted in US[26,27] reported associations based on the prevalence of any retinopathy, with certain nonglycemic factors such as hypertension, dyslipidemia, ageing and obesity. Hammes HP et al[28] also reported that hypertension was significantly associated with development of DR. Lima, V.C et al[29] reported that in their study, hypertension and dyslipidemia did not reach the statistical significance level established ($p < 0.05$).

In the right eye, out of 330 subjects 108 (32.73%) showed no signs of diabetic retinopathy with a mean HbA1c value of 8.55% and mean duration of diabetes among these was 7.19 years. While in 72(21.82%) subjects, it showed presence of proliferative diabetic retinopathy with a mean HbA1c value of 9.49% and mean duration of diabetes among these was 12.05 years. The value of R is 0.3433, co-efficient of determination: 0.1179 suggests a positive correlation between mean HbA1c and duration of diabetes and grade of diabetic retinopathy.

In the left eye, out of 330 subjects, 110(33.33%) subjects showed no signs of diabetic retinopathy with a mean HbA1c value of 8.44% and mean duration of diabetes was 7.08 years. While 70(21.21%) subjects showed signs of proliferative diabetic retinopathy with a mean HbA1c value of 9.52% and mean duration of diabetes was 12.32 years. The value of R is 0.3489, Co-efficient of determination: 0.1217 suggests a positive correlation between mean HbA1c and duration of diabetes and grade of diabetic retinopathy. In our study there is high incidence of NPDR as compared to PDR. In a study[30] involving 597 T2DM Chinese patients (29.7%) had DR, of which 548 (27.3%) were non-proliferative diabetic retinopathy and 49 (2.4%) were proliferative diabetic retinopathy. Mehta K et al.[31] reported that the prevalence of NPDR (33.98%) was higher than PDR (31.5%) in their study group. Thomas RL et al[15] assessed the global prevalence of DR from the articles published between 2015 to 2019 was 27.0% for any DR comprising of 25.2%, NPDR and 1.4% PDR signifying the higher incidence of NPDR than PDR.

Mean HbA1c value in our study was found to be 8.60%.

In our study, fasting blood sugar level was <100 in 16 patients (7 eyes had NPDR), 101-150 in 143 (131 eyes had NPDR), 151-200 in 88 (118 eyes had NPDR and 32 had PDR), 201-250 in 34 (23 eyes had NPDR and 41 had PDR), 251-300 in 30 (15 eyes had NPDR and 41 had PDR) and >300 in 19 patients (6 eyes had NPDR and 28 eyes had PDR). BSL-F >100 was found to be a risk factor for development of NPDR while >150 has shown preponderance to PDR. In Lokesh S et al. study,[16] 32% of patient had fasting blood sugars more than 200, 48% of patients had fasting blood sugars in the range of 126-199 and 20% had Fasting blood sugars less than 126.

In our study, HbA1c level was <6 in 12 patients (mean BSL-F: 138.41 mg/dl; 12 eyes had NPDR and 3 eyes had PDR), 6.0-7.0 in 62 (mean BSL–F: 135.85 mg/dl; 8 eyes had NPDR and 8 had PDR), 7.1-8.0 in 84 (mean BSL-F: 151.45 mg/dl; 87 eyes had NPDR and 21 had PDR), 8.1-9.0 in 81(mean BSL-F: 177.55 mg/dl; 87 eyes had NPDR and 39 had PDR), >9.0 in 91(mean BSL-F: 223.87 mg/dl; 55 eyes had NPDR and 71 had PDR). High HbA1c level was correlated to high BSL-F level and subsequently high number of NPDR and PDR eyes.

Diabetic control and complication trial (DCCT)[32] have shown a strong relationship between HbA1c and the development and progression of DR. Lokesh S et al study[16] showed lower frequency of DR in patients with lower HbA1c group and an increase in frequency of DR as the HbA1c increases. UKPDS land mark trial[33] also reported similar findings where intensive blood-glucose control substantially decreases the risk of microvascular complications in patients with T2DM. Khalid M et al[12] reported a strong relationship between HbA1c and development of DR ($p < 0.001$). Patients with uncontrolled diabetes had higher chances of developing DR (66.61%). Similar findings were reported by Garg Petal,[17] Long Metal[19] and Lind Metal.[34] Zhang R et al.[18] reported that when fasting plasma glucose exceeded 7.03 mmol/L and HbA1c exceeded 6.4%, the prevalence of DR increased sharply. In Asian patients with T2DM,[35] higher mean HbA1c level was associated with moderate or worse DR

(OR 2.02, 95% CI 1.31- 3.12).

5. Conclusion

Our study showed that as the HbA1c level increases prevalence of DR also increases and there is a strong relationship between HbA1c level and DR. Apart from HbA1c levels, poor control and duration of DM also showed a significant association. Advanced age, male gender, type of DM, smoking status, alcohol consumption, co-morbidities such as hypertension and dyslipidemia also showed an association with prevalence of DR.

6. Limitations

1. The study sample was small to extrapolate to regional and national trends.
2. Treatment modalities was not discussed.
3. Long term follow up and outcome of treatment modalities was not discussed.
4. Cost implications in management of diabetes and retinopathy arising thereof were not studied.

7. Source of Funding

None

8. Conflict of Interest

None.

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Cite this article: Singh C, Prasad SP, Kaul S, Motwani D, Mishra A, Padmakumar V. Association of HbA1c levels with diabetic retinopathy. *Indian J Clin Exp Ophthalmol* 2021;7(2):339-345.