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To Correlate HBA1C (Glycosylated Haemoglobin) Level in Diabetic Retinopathy Patients Suffering from Type II Diabetes Mellitus in South Indian Population.

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ABSTRACT:
Background: To assess the correlation of HbA1c (Glycosylated Haemoglobin) level in Diabetic Retinopathy patients suffering from Type II Diabetes Mellitus in South Indian population.
Material and Methods: A descriptive observational study of 500 Type II Diabetes Mellitus (DM) patients having Diabetic Retinopathy (DR) who attended Department of Ophthalmology and Department of General medicine between January 2020 to December 2022 at Gitam Institute of medical sciences and research centre(GIMSR) were taken into account. All the patients were subjected to the basic blood investigations, slit lamp examination and dilated fundus examination. The results were tabulated according to the severity of retinopathy and level of HbA1c levels.
Results: Out of 500 patients in the study, mean age of Type II diabetes patients was 52.4±8.62years, out of which 69.2% were male patients and 30.8% were female patients. The mean duration of Diabetes Mellitus was 6.50±4.63 years. The mean of HbA1c is in the study population was 8.4±1.78. Majority (45.6%) patients in the study were moderate NPDR. The severity of Diabetic Retinopathy increased with increase in the level of HbA1C level.
Conclusion: Our study showed that with increase in the level of HbA1c, the severity of the diabetic retinopathy increases. There was a positive correlation between the level of HbA1c and severity of Diabetic Retinopathy.
Key Words: Diabetes mellitus, Diabetic retinopathy, Nonproliferative daibetic retinopathy [NPDR], proliferative diabetic retinopathy [PDR], Clinically Significant Macular Edema[CSME], Glycosylated haemoglobin[HbA1c]

I. INTRODUCTION

Diabetes is the commonest metabolic abnormality in the humans. [1] It is metabolic diseases characterized by hyperglycaemia resulting from defect in insulin secretion, insulin action or both. Worldwide about 415 million people are suffering from DM, which is expected to increase to 642 million by 2040 due to uncontrolled population, more caloric consumption and sedentary lifestyle.[2]Type 2 diabetes is the commonest form of diabetes constituting nearly 90% of the diabetic population. [3]India is considered as world capital of Diabetes. The estimates in 2019 showed that 77 million individuals had diabetes in India, which is expected to rise to over 134 million by 2045.[4]

Diabetic retinopathy is among the most common causes of legal blindness affecting the age group of 20-74 years of age.[5]It is the chronic progressive sight threatening disease of retinal microvasculature associated with prolonged hyperglycemia. The presence of diabetic retinopathy indicates microcirculatory dysfunction in the other organ systems.[6]

HbA1c also called glycosylated haemoglobin is considered as the best available biochemical parameter to assess the long-term metabolic control in patients with DM. Glycosylated haemoglobin is non enzymatic addition of a sugar residue to haemoglobin. When glucose is bound non-enzymatically to a terminal portion of Hb chain, its quantization becomes possible. This measurement is directly proportional to blood glucose concentration.[7]As the life span of glycosylated haemoglobin is 120 days, unlike FBS and PPBS, it gives us a long term glycemic values. American Diabetic association is recommending fractionated value of HbA1c to be considered as the best indicator of glycemic value of past 8-12 weeks. It is chosen to help us to foresee end tissue damage and its progression. The normal value of HbA1c is < 6.9% of total haemoglobin.[8]

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

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concentration. Present study is undertaken to determine the prevalence of diabetic retinopathy in association with raised HbA1c levels and also to correlate the levels of HbA1c with the severity of diabetic retinopathy.

II. MATERIAL AND METHODS

It is a descriptive observational study of 500 Type II Diabetes Mellitus (DM) patients with Diabetic Retinopathy (DR) who attended Department of Ophthalmology and Department of General medicine between January 2020 to December 2022 at Gitam Institute of medical sciences and research centre (GIMSR) who are fitting into the inclusion criteria were included in the study.

Study Design: Descriptive observational study.

Study Location: This was a tertiary care teaching hospital based study done in Department of Ophthalmology and Department of Medicine, at Gitam Institute of medical sciences and research centre (GIMSR), Visakhapatnam, Andhra Pradesh, India.

Study Duration: January 2020 to December 2022

Sample size: 500 patients

Subjects & selection method: The study population was drawn from patients who presented to GIMSR medical college from January 2020 to December 2022 and had Diabetes Mellitus along with Diabetic Retinopathy and had undergone blood investigations like fasting blood sugars, post prandial blood sugars, HbA1c level, renal function test and dilated fundus examination.

Inclusion criteria:

1. Age >18 years
2. Patients with Type II diabetes mellitus with diabetic retinopathy changes in the fundus.
3. Fasting Blood glucose≥ 126 mg/dL [7.0mmol/L])
4. HbA1C levels ≥ 6

Exclusion criteria:

1. Patients with Type 1 diabetes mellitus
2. Gestational diabetes mellitus
3. Patients on long term steroids
4. Undergone laser photocoagulation therapy
5. Patients with dense cataracts and corneal opacities which prevented visualization of posterior segment.

Procedure methodology:

After taking an informed written consent as per the declaration of Helsinki, and an ethical clearance, all patients were examined according to a predesigned proforma. Relevant history regarding the diabetes with respect to age of onset, duration, use of oral hypoglycemic agents or Insulin, other co-morbidities like Hypertension, Coronary Artery Disease(CAD). Diabetic patients were diagnosed according to American Diabetes Association (ADA) criteria. A general physical examination was performed followed by a complete ophthalmic examination. All patients underwent biochemical tests, like complete blood counts, fasting blood sugars, post prandial blood sugars, HbA1c levels, renal function tests.

Ophthalmic examination of both the eyes included visual acuity assessment by Snellen's chart and Jaeger's chart, 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. The retinopathies were observed and documented in accordance with the modified ETDRS classification i.e. International Clinical Disease Severity Scale for Diabetic Retinopathy which has been proposed to facilitate simple to use in clinical practice. This new classification is simple to use, easy to remember and based on scientific evidence. There are five stages that are recognized. The first is "no apparent retinopathy". As the name implies there are no diabetic fundus changes. The second stage is "mild non-proliferative retinopathy" (mild NPDR). This stage is characterized by the presence of a few microaneurysms. The third stage is "moderate NPDR" which is characterized by the presence of microaneurysms, intraretinal hemorrhages or venous beading. The fourth stage is" severe NPDR" is based on the 4:2:1 rule of the ETDRS (four quadrant intraretinal haemorrhages, two quadrants or more of venous beading and one quadrant or more of IRMAs- intraretinal microvascular abnormalities). The fifth or final stage is "proliferative diabetic retinopathy" (PDR). PDR is characterized by neovascularization of the disc, neovascularization of the retina, neovascularization of the iris, neovascularization of the angle, vitreous hemorrhage or tractional retinal detachment. CSME was defined upon slit lamp biomicroscopy as "(1) thickening of the retina at or within 500 µm of the center of the macula; or (2) hard exudate at or within 500 µm of the center of the macula associated with thickening of adjacent retina; or (3) a zone of retinal thickening 1-disc area or larger, any part of which is within 1-disc diameter of the center of the macula"

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Statistical analysis:

All the data was collected, compiled and tabulated in Microsoft Excel sheet. The statistical analysis was performed using software PPSS 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.

III. RESULTS

Out of 500 patients who have diabetes with DR, the minimum age was 31 years and maximum age was 80 years with mean age of 52.4±8.62 years. 69.2%(346) were males and 30.8%(164) were females. Mean duration of diabetes mellitus was 6.50±4.63years. 85%patients were on oral hypoglycaemic agents and 15% of patients were on both oral hypoglycaemic agents and insulin. 11% of patients had coexisting hypertension (HT), 1.4 % patients had Coronary Artery Disease (CAD) and 0.2% patients had both HT and CAD. In the present study the mean HbA1c level was 8.4±1.78. 49.8% of patients had HbA1c of < 8.0, 35.2% had HbA1c between 8.0 -10.0 and 15.0% of patients had HbA1c of more than 10.0.

Majority of them had moderate diabetic retinopathy accounting for 45.6% followed by severe diabetic retinopathy in 26.2% and 20.2% patients with mild diabetic retinopathy. 7.6% of the patients had proliferative diabetic retinopathy (Table-1).13.4 %(67) patients had CSME.

Table 1: Incidence of diabetic retinopathy based on severity

DR type	Frequency	Percent
Mild	101	20.2
Moderate	228	45.6
Severe	133	26.6
PDR	38	7.6
Total	500	100.0

Table 2 shows the severity of DR with HbA1c level. Patients with Mild NPDR has mean Hba1c level 6.98±0.42, moderate NPDR with mean HbA1c 7.92±1.06, severe NPDR with mean HbA1c 9.38±1.61 and PDR with mean HbA1c 11.63±2.23.The table denotes that, the more severe is DR the higher is HbA1c level in the patients.

Table 2: Severity of DR with HbA1c level

Retinopathy	HbA1C			P-value
	N	Mean	SD	
Mild	101	6.98	0.42	0.0001
Moderate	228	7.92	1.06	
Severe	133	9.38	1.61	
PDR	38	11.63	2.23	

Table 3 shows correlation of severity of diabetic retinopathy in relation to value of HbA1c.Out of 249 patients who had HbA1c level less than 8, 92.4%(230) patients had mild to moderate NPDR. Out of 176 patients who had Hba1c level between 8 to 10, 89.4%(157) patients

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had moderate to severe NPDR.75 patients who had Hba1c level more than 10, 78.6%(59) patients had severe NPDR to PDR. This table suggests that there is a positive correlation between the level of HbA1c the severity of DR. The more is the level of Hba1c level the severe is the DR in the patient.

Table 3: Correlation of severity of diabetic retinopathy with the levels of HbA1c.

Diabetic retinopathy	**HbA1c**						**Total**	
	< 8		**8 - 10**		**> 10**			
	Count	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
Mild	**95**	**38.2%**	6	3.4%	0	0.0%	101	20.2%
Moderate	**135**	**54.2%**	**77**	**43.8%**	16	21.3%	228	45.6%
Severe	19	7.6%	**80**	**45.5%**	**34**	**45.3%**	133	26.6%
PDR	0	0.0%	13	7.4%	**25**	**33.3%**	38	7.6%
Total	249	100.0%	176	100.0%	75	100.0%	500	100.0%
P-value = 0.0001								

Table 4 shows out of 500 patients, 49%(245) patients had microalbuminuria. The mean duration of DM in those patients was 8.42± 5.42 years as compared to patients without microalbuminuria who had a mean duration of 4.66 ± 2.65 years. It clearly signifies that the more is the duration of DM more are the chances of microalbuminuria in those patients which was clinically significant.

Table 4: Correlation of Microalbuminuria and duration of DM

MIC ALB	**Duration of DM**			**P-value**
	N	**Mean**	**SD**	
Yes	245	8.42	5.42	0.0001
No	255	4.66	2.65	

Table 5 suggested that out of 500 patients who had DR, 13.4% (67) patients had CSME. When we compared the mean HbA1c level of the CSME patients, it was found that mean HbA1c level of CSME patents were significantly higher (9.85 ± 2,16) than the patients without CSME(8.18 ± 1.60).

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Table 5: Correlation of mean HbA1c level and CSME

CSME	HbA1C			P-value
	N	Mean	SD	
Yes	67	9.85	2.16	0.0001
No	433	8.18	1.60	

IV. DISCUSSION

The present study was conducted as a descriptive observational study to determine the correlation of HbA1c levels with diabetic retinopathy. The present study included 500 cases of retinopathy which constituted 20.2% mild NPDR, 45.6% moderate NPDR, 26.6 % severe NPDR and 7.6% PDR. Out of 500 retinopathy patients moderate NPDR accounted for nearly half the patients while the other half consisted of severe, mild and PDR. Regardless of the severity of retinopathy, 13.6 % cases had CSME. Indian studies like Chennai Urban Rural Epidemiological study (CURES) showed an overall prevalence of diabetic retinopathy of 17.6%[9].Chennai study revealed the prevalence of DR was 34.1%. The prevalence included 30.8% with NPDR, 3.4% with PDR and 6.4% had DME. [10]A study by Dr Prasad et all showed 17% mild NPDR, 18% moderate NPDR, 48% severe NPDR,13% PDR with 23% patients with CSME.[11]The differences in the findings could be attributed to variable population characteristics as age of onset, duration of DM, type of DM, other co morbidities like HT, CAD and treatment modalities.

In our study 69.2% were males and 30.8%were females who had DR. This was correlating with the study done by Niveditha H et al, and Gadkari SS et al.[12,13] The mean age of patients were 52.4±8.62years. Similar findings were reported by Khalid M et al[14], Zhang R[15], Long M[16] where majority of the patients were above the age of 50 years. The average duration of DM in our study was 6.50±4.63years. In the study conducted by Lokesh S et al,[17]average duration of diabetes mellitus was 9.8 ± 5.34 years. Karadeniz Z et al[18] reported that the presence and the severity of DR was increasing as the duration of DM increases. Melo L.G.N et al[19]also reported that longer duration of DM is a risk factor for development of DR. Out of 500 patients enrolled in the study, 11% (55) had hypertension, Hypertension is the most common co-morbidity in patients with DR. In Lokesh S et al. study[17]54% of patients had coexisting hypertension. Hammes HP et al[20] also reported that hypertension was significantly associated with development of DR.

The glycemic status of the patients in this study was studied by measuring HbA1c levels. The distribution of HbA1c in our study among the levels of retinopathy revealed significant transition from mild NPDR to PDR with increasing level of HbA1c (Table 3). A study done by Leske et al, in Barbodose eye study, found that every 1% increase in HbA1c from baseline was associated with a >2-fold risk of DR. In 4 years of follow up, the study showed linear relationship of HbA1c levels with the development of DR.[21]In our study, the HbA1c values were compared in the groups with increasing severity of retinopathy and increasing levels of HbA1c were noted showing a significant correlation (Table 3,4).Therefore it was noted that poor glycemic control led to the worsening of the retinopathy. Diabetic control and complication trial (DCCT)[22] have shown a strong relationship between HbA1c and the development and progression of DR. Lokesh S et al study[17] 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[23] also reported similar findings where intensive blood-glucose control substantially decreases the risk of microvascular complications in patients with T2DM.

Out of 500 DR patients 49% patients had microalbuminuria. There was a positive correlation of microalbuminuria with increased level of HbA1c level and duration of DM. Lokesh S et al study [17] showed 40% patients of DR had microalbuminuria. Manaviat MR et al[24]at Iran also conclude that microalbuminuria may be a marker for the risk of proliferative retinopathy development. As the microalbuminuria indicates renal involvement and with its correlation with coronary artery disease

and retinopathy, we consider microalbuminuria as an indicator of generalized vascular involvement in the form of endothelial dysfunction.

Comparison of the means of HbA1c in patients with and without CSME revealed statistically significant association of CSME with HbA1c. High glycosylated haemoglobin (HbA1c) level is a well-known risk factor for diabetic macular oedema. The DCCT had demonstrated that intensive treatment to maintain blood glucose levels at a normal range reduced the risk of clinically significant macular oedema at the rate of 23%.[22.] A study by Diana V Do et al[25]suggested that patients with type 2 diabetes and persistent CSME have higher HbA1c at time of their disease than patients with resolved CSME.

V.CONCLUSION

The increased level of HbA1c level showed an increasing trend as severity of diabetic retinopathy. The poor metabolic control as demonstrated by high HbA1c is significantly associated with severity of retinopathy and presence of CSME and microabluminuria. From the analysis of our study, we recommend to maintain HbA1c levels below 7.0 % which may reduce the risk of development and progression of diabetic retinopathy. Apart from HbA1c levels, poor control, duration of DM, advanced age, male gender, co-morbidities such as hypertension and CAD also showed an association with prevalence of DR.

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Ethical statement
Approval from the Institutional Ethics Committee of GIMSR (GIMSR/Admin/Ehics/ approval/IEC-56/ 2019) was obtained prior to the commencement of the study.

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Conflicts of interest
There are no conflicts of interest.

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