ORIGINAL RESEARCH

Correlation of HbA1c Level with Diabetic Macular Edema - A Clinical Study in a Tertiary Care Centre

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Received: 19 January, 2024 Accepted: 25 February, 2024

ABSTRACT
Diabetic retinopathy (DR) is one of the complications of diabetes mellitus (DM) that cause most hardship. It is the leading cause of blindness in adults of working age. Diabetic macular edema (DME) is the main cause of poor vision in patients with diabetes. In the past, DME was diagnosed by only ophthalmoscope but now with the help of optical coherence tomography (OCT), it is possible to measure the macular thickness objectively and to follow the DME progression quantitatively. Periodic glycosylated haemoglobin (HbA1c) measurements can reflect the long-term control of hyperglycemia.
This cross sectional study, conducted over a year (June 2022 to May 2023) aims to see the relationship of Diabetic Retinopathy with the status of control of diabetes, as intensive glycemic control had been proved to be effective in decreasing and progression of DR in type 1 and type 2 diabetic mellitus as demonstrated by the diabetes control and complication trials and the United Kingdom Prospective Diabetic study.
Various parameters, including Age distribution of patients, Duration of Diabetes, Presenting and Associated symptoms, Treatment Profile of Patients**,** Personal Habits, Grade of retinopathy, HbA1c levels and the foveal thickness, were assessed. Results revealed higher HbA1c levels were significantly associated with the development of CSME in patients with diabetic retinopathy p value showing 0.0048. The study highlights the importance of periodic evaluation of glycemic control with routine glycosylated haemoglobin measurements may help optimise visual outcome in diabetic subjects.

INTRODUCTION

The term “Diabetes Mellitus” describes a metabolic disorder and alteration of carbohydrate, fat and protein metabolism. The etiopathogenesis is usually multifactorial and may result in the defects in insulin secretion, insulin action or both. The disease has already acquired the status of a global pandemic. The growing public health burden of diabetes across the world is reflected in the prevalence of the disease which has a expectation to rise from 171 million in 2000 to 366 million in 2030[1] . According to the Diabetes Atlas 2021 published by the International Diabetes Federation, the number of people suffering with diabetes in India currently around 74.1 million[2]. India is now called the “Diabetic Capital of the World”.

Diabetic retionopathy (DR) Aand diabetic macular edema (DME) are very common microvascular complications in patients who have diabetes and may have a sudden and debilitating effect on visual acuity (VA), eventually leading to permanent blindness. Diabetic Macular edema which is manifested as retinal thickening primarily due to exudaton from incompetent macular capillaries, is the most common cause of moderate visual loss (MVL) (defined as a doubling of the visual angel, for example ,20/40 to 20/80 or a loss of 15 or more letters on the ETDRS chart) in people with diabetes mellitus[3]. According to the ETDRS, the 3 years risks of MVL in untreated patients suffering from CSME was 33%.[4]

The prevalence of diabetes is relentlessly, particularly in working-age adults. Approximately one-half of individuals with diabetes will develop retinopathy in time. The prevalence of DME is very high among diabetic population. This is reflected from overall prevalence of 11.1% among the patients who has diabetes in Wisconsin Epidemiologic study of Diabetic Retinopathy. The long-term incidence of macular edema over 10 years in the WESDR was 20.1% in the younger onset group, 13.9% in the older onset group not taking insulin, to as high as 25.4% in the older onset group taking insulin.[5] The level of

glycemic control in patients with diabetes has been linked with the occurrence of diabetic retinopathy. It is partly possible to evaluate the glycemic control in patients by measuring the glycosylated haemoglobin level (HbA1c) which gives a clue about the average blood glucose levels over the past twelve weeks. The WESDR[5] showed that a 1% decrease in the level of HbA1c from the baseline to the 4 year follow up would be expected to lead to a 25% reduction in the 10 year incidence of macular edema.

Diabetic macular edema is diagnosed clinically by stereoscopic slit lamp biomicroscopy using preferably a contact lens for fundus examination. However, this method lacks the ability to quantify macular edema and has a limited sensitivity and specificity in diagnosing early and mild cases. Fluorescein angiography may be useful for evaluating the severity of the dysfunction of blood-retinal barrier; however, it does not reliably quantify the degree of fluid accumulation in retina. The Optical Coherence Tomography (OCT) is a newer modality that helps in objective assessment of diabetic retinopathy. It was first described by Huang et al in 1991[6]. Moreover, OCT is found to be helpful in the morphological description of diabetic macular edema.

Five distinct patterns of CSME have been defined based on OCT[7]:

1. Sponge like retinal Thickening
2. Cystoid Maculae Edema.
3. Serous Retinal Detachment.
4. Taut Posterior Hyaloid Membrane.
5. Foveal Tractional Retinal Detachment.

Evidence that OCT allows not only the qualitative diagnosis of Diabetic Retinopathy but also the quantitative assessment of the edema has come from different studies.

Therefore to see the relationship of Diabetic Retinopathy with the status of control of diabetes, the study was undertaken with the following aims and objectives:

1) To study the correlation of glycosylated haemoglobin level and diabetic macular edema.

2) Qualitative and quantitative assessment of macular edema using OCT and to correlate the foveal thickness and HbA1c level.

MATERIALS AND METHODS

This cross sectional study titled – **" A CLINICAL STUDY ON ASSOCIATION OF GLYCOSYLATED HEMOGLOBIN LEVEL WITH DIABETIC MACULAR EDEMA"** was conducted in the Regional Institute of Ophthalmology, Guwahati Medical College and Hospital, during the period of June 2022 to May 2023 in collaboration with department of Biochemistry and Endocrinology.

We divided the patients into two groups based on the presence of diabetic edema.

Group 1: Included 70 patients having Diabetic Clinically Significant Macular Edema (CSME) in at least one eye. (Diagnosed according to the ETDRS criteria).

Group 2: Included 70 patients of Diabetic Retiinopathy without macular edema in either eye.

Therefore, a total of 140 patients were taken up for this study.

SELECTION OF CASES

The patients were selected from the outdoor as well as indoor of RIO, Guwahati. Informed consent was obtained from each of the patients after explaining the purpose of the study design.

INCLUSION CRITERIA

1. Diabetic patients as diagnosed by the ADA Guidelines 2021 having various grades of retinopathy were included.
2. Both sexes were included.
3. Age between 10-70 years.

EXCLUSION CRITERIA

1. Patients with media opacity.
2. Patients of Ocular trauma
3. Past history of intraocular surgery.
4. Patients with Retinal Detachment or other Chorioretinal inflammatory process.
5. Pregnancy.
6. Patients having severe nephropathy with fluid retention or on dialysis.
7. Patients with history of Retinal Photocoagulation.
8. Patients with uncontrolled hypertension.
9. Severe Anemia.

A complete **history** was taken and due importance was given to the following points:

1. Age, Sex.
2. Details of the complaints
3. Type and duration of DM.
4. Treatment history
5. Other Associated diseases.
6. Personal history and
7. Relevant family history.

Systemic examination: Was done for all cases including General Examination and systemic examination and signs of any complications of diabetes were noted.

Ocular examination: was done very meticulously in every patients with the following emphasis:

1. *Visual Acuity,* both for near and distance, including pin-hole and best corrected visual acuity was done with standard Snellen's chart and Near vision chart for both eyes.
2. *Intraocular Pressure* was recorded using Non contact tonometer in both eyes.
3. Detailed *Slit Lamp Examination* was done to note any anterior segment pathology.
4. The pupils were dilated with Tropicamide 0.8% and Phenylephrine 5% eye drop (1 drop thrice, at

15 minutes interval) and detailed posterior segment examination was carried out with:

- Direct Ophthalmoscopy for generalized view of the posterior pole.
- Slit lamp Biomicroscopy with 90 D Lens for detailed posterior pole and vitreous examination.
- Indirect Ophthalmoscopy for peripheral retinal examination was done

5. Fundus Photographs were taken in the Fundus camera and grading of retinopathy was done. CSME was diagnosed according to the ETDRS criteria. The patients were divided into 2 groups those havind DR and those without DR in either eye.
6. OCT imaging was performed using the Stratus OCT machine model 3000 (Carl Zeiss Meditec Inc.) with software version 4.0, which provides an axial resoluition of less tham 10µm. The Fast Macular thickness protocol was used. This protocol uses six, high speed 6-mm radial lines (oriented 30 degree apart) to delineate macular anatomy and pathology. The protocol enabled all six lines to be acquired in a continuous, automated sequence within 1.92 seconds, with each of the six lines composed of 128 equally sapced transverse sampled locations (total of 128 ×6 lines or 768 sampled points). Because of its short acquisition time, tha fast macular thickness protocol is believed to be less prone to errors caused by unstable fixation, an important consideration in the assessment of patients with Diabetic macular edema.

The patients was aligned correctly with the OCT machine and was asked to look at an internal light. It was ensured that the scans were taken through fovea. Low quality scans with low signal strength, scans with artifacts were discarded. Only the high quality, well-centered scans with signal strength more than 6 were saved.

Each scan was analysed using the onboard Stratus OCT software (Version 4.0) with segmentation of retinal layers and qualitative and quantitative assessment of retinal layers.

7. Fundus Fluorescein Angiography (FFA) was then done:

Fluorescein angiography was done whenever indicated, using the Zeiss Visucam fundus photograph camera with fully dilated pupils after receiving an informed consent from the patients.

LABORATORY INVESTIGATIONS

1.) Routine examination (R/E) of blood: The blood was examined for the following:

- Hemoglobin estimation by Sahil (acid hematin) method.
- Total leucocyte count by hemocytometry.
- Differential leucocyte count
- Erythrocyte sedimentation rate by Westergren's method.

2.) Routine examination of urine for sugar, albumin, pus cells, casts, RBC's.

3.) Serum separation was done for some investigations stated below. About 6 to 10 ml. Of fresh venous blood was collected by disposable syringe from the median cubital vein and carried to the laboratory in plain sterile vials. The blood was allowed to clot for 20-25 minutes and the separated serum was centrifuged. All biochemical estimations were done by using calorimetric principle in an automated analyzer. The serum was used for the following tests:

- Estimation of fasting blood glucose (after 12 hours of overnight fasting) and postprandial blood glucose (after 2 hours of mid day meal).
- Estimation of serum creatinine.
- Estimation of Glycosylated Hemoglobin.

Estimation of Glycosylated Hemoglobin

Glycosylated Hemoglobin (HbA1c) estimation was carried out by a modified calorimetric method of Fluckiger and Winterhalter. 5 ml heparinised venous blood was centrifuged to collect RBC's. The packed cells were washed 3-4 times in normal saline. After final wash 0.5ml of CC14 were added and mixed vigorously then centrifuged. The supernatant hemolysate were separated and its haemoglobin concentration was adjusted to 10gm% with distilled water. To 2ml of hemosylate, 1ml of 0.3 N oxalic Acid was added and heated in incubator at 1000C for 60 mins. After cooling 1ml 40% T.C.A was added., shaken vigorously and centrifuged. To 2ml of this supernatant 0.5 ml of 0.05 M thiobarbituric acid was added and incubated at 370C for 30 min. The resultant yellow colour was read on colorimeterat 443nm, HbA1c was calculated on assumption that 1% HbA1c corresponds to an absorbance of 0.029 at 443 nm.in general, the reference range (that is found in healthy persons) is about 4% to 5.9%.

We compared the glycosylated haemoglobin levels between the 2 groups. The statistical analysis was done using unpaired t test with Welch correction, (t=2.876, 121 degrees of freedom).

RESULTS AND OBSERVATIONS

Table 1: Table shows Age distribution of patients in the two groups:

	Group 1			Group 2		
Age Distribution	**Total**	**Males**	**Females**	**Total**	**Males**	**Females**
<20 years	0(0.00%)	0(0.00%)	0(0.00%)	1(1.43%)	1(1.43%)	0(0.00%)
20-29 years	2(2.86%)	1(1.43%)	1(1.43%)	0(0.00%)	0(0.00%)	0(0.00%)

30-39 years	5(7.14%)	3(4.28%)	2(2.86%)	5(7.14%)	4(5.72%)	1(1.42%)
40-49 years	14(20%)	12(17.14%)	2(2.86%)	26(37.14%)	22(31.43%)	4(5.71%)
50-59 years	32(45.71%)	25(35.71%)	7(10%)	25(35.71%)	16(22.85%)	9(12.86%)
≥ 60 years	17(24.28%)	15(21.43%)	2(2.86%)	13(18.57%)	8(11.43%)	5(7.14%)

Table 2: Duration of Diabetes:

	Group 1		Group 2	
Duration of Diabetes	**No. Of patients**	**Percentage**	**No. Of patients**	**Percentage**
<5 years	8	11.43%	14	20%
5- <10 years	15	21.43%	25	35.71%
10-<15 years	29	41.43%	21	30%
≥ 15 years	18	25.71%	10	14.29%

Table 3: Presenting and Associated symptoms:

	Group 1		Group 2	
Presenting symptoms	**No. Of patients**	**Percentage**	**No. Of patients**	**Percentage**
General dimness of vision	66	94.29%	56	80%
Distorted images	27	38.57%	0	0.00%
Central dimness of vision	17	24.28%	0	0.00%
Headache	2	2.85%	7	10%
Watering	3	4.28%	6	8.57%
Routine exam	0	0.00%	6	8.57%

Table 4: Treatment Profile of Patients:

	Group 1		Group 2	
Drugs	**No. Of Patients**	**Percentage**	**No. Of Patients**	**Percentage**
Diet + Exercise	2	2.85%	6	8.57%
Insulin	21	30%	11	15.71%
OHA	34	48.57%	43	61.43%
OHA+Insulin	13	18.57%	10	14.23%
Antihypertensive	31	44.28%	22	31.43%
Aspirin	6	8.57%	**6**	8.57%

Table 5: Personal Habits:

	Group 1		Group 2	
Personal habits	**No. Of patients**	**Percentage**	**No. Of patients**	**Percentage**
SMOKING	13	18.57%	14	20%
ALCOHOL	17	24.29%	16	22.86%
TOBACCO	16	22.86%	14	20%

Table 6: Grade of retinopathy in the two groups:

	Group 1		Group 2	
Grade	**NO. Of patients**	**Percentage**	**No. Of patients**	**Percentage**
Mild NPDR	2	2.86%	18	25.71%
Moderate NPDR	41	58.57%	47	67.14%
Severe-very severe NPDR	14	20%	3	4.29%
PDR	13	18.57%	2	2.86%

Table 7: HbA1c levels and CSME and non-CSME group:

	Group 1 (CSDME)	Group 2 (No CSME)
No. Of patients	70	70
Mean HbA1c	9.343	8.427
SD	±2.200	±1.503
SEM	0.2629	0.1796
Unpaired t test	t=2.876, 121 degrees of freedom. P=0.0048	

Table 8: HbA1c levels and the foveal thickness

	HbA1c	Foveal Thickness
Mean	9.343	369.69
Standard deviation	±2.200	±71.814
Minimum	5.9	266
Maximum	15.3	542

DISCUSSION

- In our study the Mean ± SD HbA1c in Group 1 (CSDME) was 9.343 ± 2.200 and in Group 2 it was 8.427 ± 1.503 and p value is 0.0047 consider very significant. Similar results were obtained in the other studies in **WESDR[8].**
- **Knudsen S T et al (2002)[9],** found that type 2 DM patients with diabetic maculopathy had higher HbA1c (8.5±1.5 vs 7.4±1.2%, P <0.05) than patients without retinopathy.
- **Asensio-Sanchez V M et al. (2008)[10]** found that high level of HbA1c was significantly associated with CSME, with the risk increasing more than double (2.4) for each 1% elevation of HbA1c.
- We correlated the foveal thickness in DME with the HbA1c levels. Following results were obtained on applying the Pearson correlation test: Correlation coefficient = 0.2258 p value is 0.0602, consider not quite significant. Similar correlation was done in other studies, **TH Chou et al (2009)[11]**
- In the present study, in Group 1, 14 (20%) were females, and 56(80%) were males. In Group 2, 19 (27.14%) were females and 51 (72.86%) were males. **Vitale S et al. (1995)[12]** found an association with male sex.
- In our study Mild NPDR was present in 2.86% in Group 1 and 25.71% in Group 2. Moderate NPDR in both groups , that is, 58.57% and 67.14% respectively. Severe NPDR 20% and 4.29% in both groups. PDR 18.57% and 2.86% in both groups respectively. In a study by **Yeung L et al (2009)[13],** 64.4% of the eyes with macular edema had NPDR and 35.6% eyes had PDR

CONCLUSION

- Hyperglycemia is the most important modifiable risk factor associated with diabetes. There has been a more widespread availability and standardization of the HbA1c assays in the recent years.
- Higher mean glycosylated haemoglobin levels are very significantly associated with the development of macular edema in patients with diabetic retinopathy.
- Also, Glycosylated haemoglobin levels have a positive correlation with the foveal thickness on OCT, though not found to be satistically significant in our study.
- Even as new risk factors and mechanisms of the disease come into light, the most important still remains the level of glycemic control, periodic evaluation of which with routine glycosylated haemoglobin measurements may help optimise visual outcome in diabetic subjects.

DISCLOSURE

- CONFLICT OF INTEREST : NIL
- FINANCIAL SUPPORT: NIL

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