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Association of Level of HbA1c with Severity of Diabetic Retinopathy

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Abstract
Introduction: *Diabetes is a major Global health epidemic. WHO predicted India to be Diabetic capital of the world. Diabetic Retinopathy arises as chronic microvascular complications of diabetes. Various factors regulate the progression of the disease. The prime systemic risk factor is hyperglycemia. This study was aimed to assess the association of HbA1c level with severity of retinopathy.*
Methodology: *Randomly selected type 2 diabetic patients at Goma Bai Netralaya of Neemuch, M.P., were examined for retinopathy by retina specialists and HbA1c was determined clinically. Analysis of variance test was used to determine the relationship between HbA1c and severity of retinopathy*
Results: *Prevalence of retinopathy was found higher in NPDR (43.75%) group than PDR (37.54%). Normal range of was kept as<7 %. HbA1c values showed significant difference between NPDR and PDR than controls. Analysis of variance for HbA1c with different groups of retinopathy is highly significant ($p<0.01$).*
Conclusion: *The value of glycosylated haemoglobin showed an increasing trend with increase of severity of diabetic retinopathy. Good glycemic control of diabetes with target HbA1c of 7.0% and regular Ophthalmic screening for diabetic retinopathy changes will reduce morbidity due to diabetic retinopathy.*
Keywords: *Microvascular, Diabetic Retinopathy, Hyperglycemia, Glycosylated haemoglobin,*

Introduction

Diabetes is a major metabolic disorder that affects a significant fraction of the population and has become a major health epidemic. The prominent characteristic of diabetes is the elevated amount of blood glucose that can result from a variety of reasons. It occurs when the body fails to produce sufficient amount of insulin or exhibits insulin resistance. Diabetes is very common condition in India and the number of diabetics is steadily increasing owing to the sedentary lifestyle of people. Further, WHO has already depicted India to be diabetic capital of the world? Persistent high levels of glucose in blood lead to diabetes which, if not controlled can lead to severe complications. It is slowly becoming a health, social and economic burden in developing countries.

This has created a need for awareness for regular diabetic screening and proper preventive programs. This can help in controlling the after

effect complications of diabetes such a microvascular as well as macro vascular complications. Diabetic retinopathy arises as a chronic microvascular complication of diabetes. If left untreated, the condition progresses to severe stages. Early detection and diagnosis is necessary if the disease is to be treated and kept in tolerable limits. There are many factors that are associated with the disease: demographic factors (which include age, sex of an individual, type and duration of diabetes in consideration), systemic factors and various growth factors that regulate the progression of the disease.

Advanced glycation end products (including glycosylated haemoglobin, HbA1c) are known to produce micro-vascular complications in diabetic retinopathy. HbA1c has long been known to predict the incidence and progression of DR. Higher amounts of HbA1c in diabetic patients, indicating poorer control of blood glucose levels, have been associated with diabetic complications like; cardiovascular disease, nephropathy, and retinopathy. The amount of glycated haemoglobin (HbA1c) reflects the glycaemic control of a patient during the 6 – 8 weeks period before testing blood sample. The amount of HbA1c correlates well with fasting and postprandial blood glucose levels. Glycated haemoglobin which has an average lifetime of 120 days, and whose blood level, therefore, represents the average blood glucose concentration for that period of time.

N terminal Valine residue of erythrocyte haemoglobin become irreversibly glycosylated in proportion to circulating glucose concentrations and the resultant product is referred to as haemoglobin A1C (HbA1c). Glycated haemoglobin levels are usually expressed as the percentage of total haemoglobin, either as the percentage of total glycated haemoglobin, or as the percentage of its largest fraction, haemoglobin A1c (usually abbreviated HbA1c; other, lesser, glycated fractions are HbA1a and HbA1b) period, the level of HbA1c is usually about two percentage points lower than that of total glycated haemoglobin. HbA1c levels in nondiabetic humans range between 4% and 6%, and the risk for development of the microvascular complications of diabetes (retinopathy, nephropathy, and neuropathy).

Glycosylated haemoglobin (HbA1c) is routinely used as a marker to indicate long-term glycemic control. The associations between high glucose levels and diabetic retinopathy have been the basis for the diagnosis of diabetes. At present HbA1c is the best surrogate marker we have for setting goals of treatment. (Glycosylated Haemoglobin, HbA1c.http://clinlabnavi-gator.com/test)

Landmark clinical trial (DCCT and UKPDS) cemented the clinical utility of HbA1c as a tool to assess the risk of diabetes complications that confirmed the relationship between the HbA1c and micro vascular complication risk existed in type 2 patients

The target for good glycaemic control recommended by the American Diabetes Association (ADA) is glycated haemoglobin A1C (HbA1c) < 7.0% to diagnose prediabetics and diabetics. It is now proven that good diabetic control may slow the development and progression of diabetic retinopathy in both type 1 and type 2 Diabetes. It can be performed at any time of the day and does not require any special preparation such as fasting. These properties have made it the preferred test for assessing glycaemic control in people with diabetes. The American Diabetes Association guidelines suggest that the HbA1c test can be performed at least two times a year in patients with diabetes that are meeting treatment goals.

As the life span of glycosylated HB is 120 days, unlike FBS and PPBS, it gives us a long term glycemicvalues. As it is 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 relationship between glucose control and development of diabetic complications remains an area of active investigation. As the relationship between HbA1c and risk of microvascular complications is exponential with

no obvious "threshold" value, it means that targets aimed for are still to some extent arbitrary.

Earlier reports showed that the prevalence of DR significantly increased at HbA1c value between 6.0% and 7.0%. Later, a value of 6.5% was seen to be a cut-off which could detect at least moderate retinopathy. HbA1c of 6.5% has now been seen as sufficiently sensitive and specific to identify individuals who are at risk of developing DR. However, it has still not proven to be an absolute cut-off threshold between normal glycemia and diabetes.

An alarming rise in diabetes and related complications is a matter of concern for socio economic health, this study was undertaken to assess association of glycated haemoglobin (HbA1c) with the severity of diabetic retinopathy.

Methodology

The present study was carried out to study severity of diabetic retinopathy in patient of type 2 Diabetes Mellitus with the levels of HbA1c at Goma Bai Netralaya, Neemuch. 80 patients confirmed with type2 diabetics were examined for symptoms of retinopathy. The study was undertaken for less than minimal risk involved as per ICMR Guidelines and recommendation of Ethical Committee of the institute. Informed consent was taken while completing the screening form. After having demographic details in a designed screening form, clinical and retinal evaluations were done by experts. Grading of retinopathy was done into NPDR and PDR groups. 15 diabetics without retinopathy were included as controls. The prevalence of DR in the study population was estimated, Glycosylated haemoglobin (HbA1c) was measured by micro auto analyzer set. According to the level of HbA1C, patients were grouped into Normal (very good control group with HbA1C<7), good control group (HbA1C between 7 and8) and poor control group (HbA1C>8). Relationship between glycosylated haemoglobin and severity of diabetic retinopathy assessed. It is expressed in percentages. Patients with other associated morbidities such as hypertension were excluded from the study. After confirmation of normal distribution for all variables, the significance of differences was evaluated by paired t-test). Analysis of variance test was used to determine the relationship between HbA1cand severity of retinopathy in patients of type 2 DM. Data are expressed as mean SD, and a value of $P<0.05$ was the criterion for statistical significance.

Observations and Results

Table1: Prevalence of retinopathy among the group

Retinopathy	No of patients	%
No DR	15	18.75%
NPDR	35	43.75%
PDR	30	37.54%

Table 1 shows prevalence of retinopathy. Out of total 80 studied diabetic patients, 35 patients (43.75%) were identified in NPDR group and 37.54% were PDR patients.15 patients with 18.75% were included as control, did not show any signs of retinopathy (No DR). NPDR accounted for nearly 81% retinopathy patients while the PDR consisted of remaining 19%, the former being higher than the later. Prevalence of retinopathy is 64.8% in relation to HbA1c.

Normal range of HbA1c was taken < 7 (ADA Guidelines).

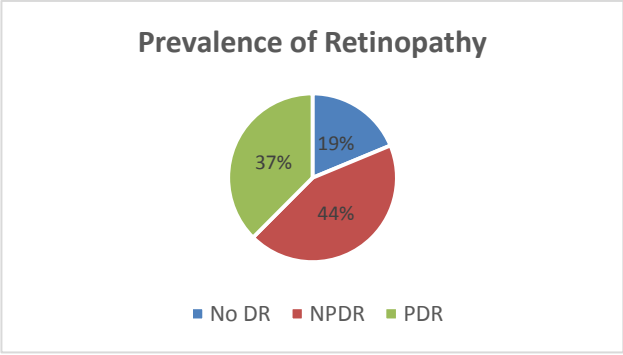

Figure 1: Prevalence of retinopathy

Table 2: Relation of HbA1c level with severity of diabetic retinopathy

Hba1c level	No DR	NPDR	PDR
< 7 Normal	9 (60%)	10 (28.5%)	0
7-8 Good	5 (40%)	20 (57.4%)	15 (50%)
>8 Poor	0 (0%)	05(14.28%)	15 (50%)

Table 2 shows the levels of HbA1c in the studied group. About 28.58% of the NPDR patient and

60% of No DR patients were in normal < 7 range. This 28.5% of NPDR increased to 57.41% in good control range 7-8 of HbA1c with 50% of PDR and 40% of No DR. > 8 shows poor control of HbA1c, 14.28% diabetic patients without retinopathy had poor control of HbA1c.50% PDR and 18.4% NPDR and 40% No DR had been found with poor control > 8 HbA1c values. HbA1c level showed significant difference between the DR cases and controls with a higher HbA1c in DR than controls.

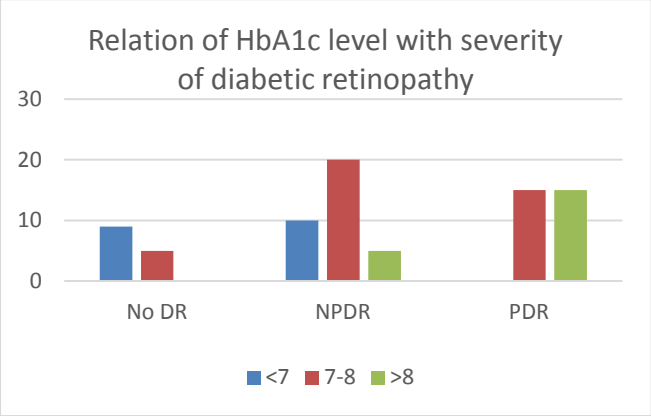

Figure 2: Relation of HbA1c level with severity of diabetic retinopathy

Table 3: Showing Means and SDs in the study group (in each level of retinopathy)

Grading of Retinopathy	Mean	SD
Non Proliferative Retinopathy	7.21	2.70
Proliferative Retinopathy	7.91	2.82
No Retinopathy	6.56	2.57

Table 3 is showing Means and SDs in the studied group. The mean of HbA1c in No DR was 6.56, in NPDR 7.21 and 7.91 in PDR group. Therefore, as the severity of retinopathy increased, the mean HbA1c for the level of severity also increased. Glycated hemoglobin concentration was significantly elevated in NPDR and PDR than No DR group. Higher concentration was found in PDR patients with a mean value of ranging from 7.91 with highest SD as 2.82 and mean of NPDR 7.21 with SD 2.7. of shows that the deviation of this concentration can lead to proliferative phase and at the same time can be reduced to Normal vision.

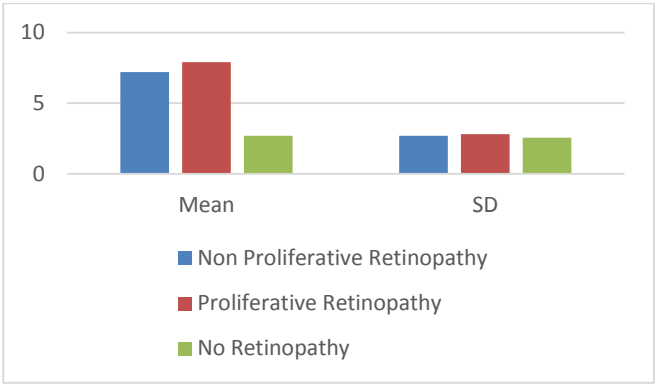

Figure 3: Means and SDs in the study group

Table 4: Analysis of Variance

Source of Variance	Sum of Squares	d.f.	Mean Squares	F
Between Groups	19.44	2	9.72	335.236
Within Groups	21.24	77	0.28	

P Value=4.88(>.01)

Table 4 shows Analysis of variance for HbA1c with different groups of retinopathy. Mean squares of retinopathy in different groups are 9.72 and within the group is 0.28. F Ratio 35.236 ratio is highly significant at p>0.01 level of confidence.

Discussion

Hyperglycemia, as measured by HbA1c, is considered an important risk factor associated with DR and it was significantly associated with retinopathy in our study.

The study consisted of 43.75% NPDR group and 37.54% PDR patients. Prevalence of retinopathy is higher as in Chennai study which revealed the prevalence of DR was 34.1% in which 30.8% with NPDR, 3.4% with PDR and 6.4% had DME.

As a glycemic indicator, higher levels of glycated haemoglobin (HbA1c) was found to be related to higher frequency of retinopathy. HbA1c values> 7.0% showed significant difference between affected patients and controls with a higher HbA1c in NPDR with 7.2 mean and PDR with 7.9 mean cases than controls with 6.5 in our study. About half patients of PDR are in good control group and other half with good control suggests that raised HbA1c is associated with an increase in sight threatening Proliferative disease.

Previous studies have shown that patients with HbA1C >8% are at higher risk for retinal diseases

confirms uncontrolled HbA1C's relation with diabetic retinopathy. We found a strong association of HbA1c with the development of any type of retinopathy.

The Table is showing the observations of glycated haemoglobin measurements and the means of HbA1c in each level of retinopathy. Glycemic control was good with a mean HbA1c of 7.21 in NPDR group. One-way distribution of HbA1c in our study among the levels of retinopathy revealed significant non homogeneity and further revealed that the transition from NPDR to PDR was statistically highly significant. This is because of increased oxygen binding capacity of HbA1c leading to hypoxia. Higher values of PDR patients are beyond the Normal Value <7% of our study, approving Poor glycemic control and worsening of the disease.

The mean HbA1c level in patients without diabetes retinopathy was 6.56 ±2.57 suggests good control of sugar. This normal level 6.5% has now been seen as sufficiently sensitive to identify individuals who are at risk of developing DR. Our data show a strong positive metabolic control of patients with DR patients reflected by low HbA1c concentrations in DR groups. This fact is reinforced by the fact that the mean glycated haemoglobin was 7.9 was beyond the recommended < 7 % of the normal values in our study.

Many studies on DR have documented the close association of chronic hyperglycemia (with high HbA1c) and the development of the retinopathy. Our findings were consistent with the DCCT study (1993), UKPDS, Klein and Klein, (1993), Rema *et al* (1996), Rema, Shanthirani et *al* (2000), Noël Vat, Wong et al (2016), Venkateswarulu M, Siva Prabodh (2011), Mohamed et al (2007). These studies suggested tight glycemic control measured by HbA1c is strongly associated with a decreased prevalence of retinopathy. Anitha et al. also found an association of advanced glycation index (AGI) with the severity of DR

DCCT showed 76% reduction in the rate of development of any retinopathy and an 80% reduction in progression of established retinopathy in patients with strict control of diabetes[1]. Wisconsin epidemiological study of diabetic retinopathy showed a positive correlation between severity of retinopathy and high level of HbA1C after 10 years of diabetes mellitus. In the CURES Eye study, for every 2 % elevation of HbA1C, the risk of diabetic retinopathy increases by a factor of 1.71, 10. In the UKPDS, the risk reduction in eye complications for every 1% decrease in HbA1C was 19%.

Previous studies recommended HbA1c level of 7% is ideal in reducing progression of and new development of diabetic retinopathy.Elevated HbA1c of PDR in our study is consistent with few remarkable studies, as it reflects poorly controlled diabetes, which is one of the major causes of complications in DM including diabetic retinopathy. (DCCT research group 1998, 2000), (UKPDS 1998).

Conclusion

The value of glycosylated haemoglobin showed an increasing trend as severity of diabetic retinopathy increases Good glycemic control of diabetes with target HbA1c of 7.0% and regular Ophthalmic screening for diabetic retinopathy changes will reduce morbidity due to diabetic retinopathy. We recommend maintaining HbA1c levels below 7.5% which may reduce the risk of development and progression of diabetic retinopathy.

Our findings, probably, may prove beneficial in organizing targeted screening programs in subjects with Diabetes withHbA1c >7.5, which would help in reducing the sight threatening retinopathy. Although the current cost of HbA1c is higher than FPG, the additional benefits in predicting costly preventable clinical complications may make this a cost-effective choice.

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