Clinical Study on Correlation of HbA1c with Different Grades of Diabetic Retinopathy at S.V.R.R.G.G.H, Tirupati – A Hospital Based Descriptive Correlative Study

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ABSTRACT

BACKGROUND
Patients with diabetic retinopathy (DR) are 25 times more likely to become blind than non-diabetics.¹ One of the main difficulties in establishing a relationship between the degree of hyperglycemia and the long-term complications of diabetes is the lack of a reliable and objective method for the assessment of diabetic control. Recordings of glycated proteins, serum proteins, and primary hemoglobin, have added a new dimension to glycemia assessment. HbA1c has been known to be a marker to assess the long-term control of diabetes mellitus. Few studies have shown the correlation between HbA1c and different grades of DR in the past. The purpose of this study was to determine the correlation of HbA1c with different grades of diabetic retinopathy.

METHODS
A descriptive correlative study was conducted among 100 diabetic patients attending the Department of Ophthalmology in S.V.R.R.G.G. Hospital, Tirupathi, for a duration of one year. Relevant history regarding their diabetes was noted. The status of diabetic retinopathy in each patient was diagnosed by comprehensive ophthalmologic examination and classified according to the early treatment diabetic retinopathy study (ETDRS) system. Patients were evaluated for their HbA1c levels.

RESULTS
Out of 100 patients, 43% of participants were females, and the remaining 57% were males. A statistically significant correlation was found between different grades of diabetic retinopathy and HbA1c levels. The other factor which had a significant correlation was the duration of diabetes and grade of retinopathy (P-value < 0.05). Age of the patient, gender of the patient, did not significantly correlate when compared in different grades of diabetic retinopathy (P-value > 0.05).

CONCLUSIONS
A statistically significant correlation was found between HbA1c levels and the severity of diabetic retinopathy. Higher the level of HbA1c (indicating poor glycaemic control), the more severe is the grade of DR in those set of patients.

KEYWORDS
Diabetic Retinopathy, HbA1c, CSME
Eye is a sophisticated biological device that functions like a camera, converting visible light into electro-chemical impulses to be processed by the brain. The coloured iris acts as a shutter, regulates the amount of light entering the eye. The transparent cornea and crystalline lens focus light rays onto the retina. Impulses are transmitted from retina to brain by means of the optic nerve. The brain then processes this information into an understandable, recognizable image. The retina is affected by many systemic disorders, one of which is diabetes mellitus (DM). An exponential increase in the global number of diabetic patients coupled with a rise in life expectancy due to better medical care has resulted in a proportionate growth in long term vascular complications such as diabetic retinopathy.

Diabetes mellitus is a major cause of avoidable blindness in both the developed as well as developing countries. Patients with DR are 25 times more likely to become blind than non-diabetics. It is estimated that diabetes mellitus affects 4 percent of the world's population, almost half of whom have some degree of DR at any given time. Patients with type 1 diabetes may show evidence of retinopathy as early as five years, after the onset of diabetes, and almost all patients will show varying degrees of retinopathy 20 years after the onset of diabetes. DR may even be present at the time of diagnosis of type 2 DM patients, consistent with the usual long duration of subclinical hyperglycaemia in such patients and more than 60 % of type 2 diabetic patients will have some degree of retinopathy after 20 years of onset of diabetes. One of the main difficulties in establishing a relationship between the degree of hyperglycaemia and the long-term complications of diabetes is the lack of a reliable and objective method for the assessment of diabetic control. Blood and urine glucose testing and urine ketone testing provide information for the usual day to day monitoring of control of diabetes. However, these tests cannot provide the patient and the health care team with a quantitative and reliable measure of glycaemic control over an extended period of time. But, recordings of glycated proteins, primary haemoglobin, and serum proteins have added a new dimension to the assessment of glycemia. With a single measurement of glycated protein of haemoglobin, we can get a quantitative estimate of the average glycemia over weeks and months, thereby complementing day to day testing.

HbA1c has been known to be a marker to assess the long-term control of diabetes mellitus. Studies in the past have shown that HbA1c levels could be correlated with the severity of DR as well. But few studies have shown the correlation between HbA1c and different grades of DR. In this study we wanted to evaluate the correlation of HbA1c with different grades of diabetic retinopathy.

**METHODS**

It is a descriptive correlative study. This study was done on 100 diabetes patients who were referred for evaluation of DR to the Department of Ophthalmology at Sri Venkateshwara medical college. The study was conducted for a period of one year from December 2019 to November 2020.

**Inclusion Criteria**
- Patients of either sex.
- Patients diagnosed as cases of diabetes mellitus of at least one-year duration on treatment with oral hypoglycaemic agents / insulin.
- Both type 1 and type 2 diabetes mellitus.

**Exclusion Criteria**
- Patients not diagnosed as having diabetes mellitus.
- Diabetic patients without retinopathy.
- Patients with ocular media opacity in both eyes so as to interfere with a detailed examination of the fundus.
- Patients with pre-existing non-diabetic maculopathy (like that due to central serous retinopathy, age-related macular degeneration, drug-induced, and other macular degenerations).
- Patients who have undergone laser photoagulation therapy.

With the Institutional ethics committee approval, informed and written consent was taken from patients in her/his vernacular language. Relevant history regarding the patient’s diabetes was taken:
- Age of onset of diabetes (first diagnosed)
- Duration of diabetes
- Nature and duration of treatment received
- History regarding patient’s glycaemic control and compliance to the treatment.

The patient’s examination was then performed as per the proforma. A general physical examination was performed, followed by a complete ophthalmological examination.

The fundus examination was done by:
- Direct opthalmoscopy
- Indirect opthalmoscopy
- Slit-lamp biomicroscopy using a + 90 D lens.
- Fundus fluorescein angiography was performed only when clinically necessary. (Suspected cases of CSME)

Based on the ETDRS criteria, patients were graded according to the severity of their retinopathy.
In the case of patients with asymmetric fundus findings, the eye with a more severe grade of DR was taken into consideration. HbA1c levels were determined for all the patients by the immuno-inhibition technique. The cut off values for normal were taken as HbA1c levels between 4.5 and 5.7 %.

Sample Size Calculation
We calculated the sample size for this study using the formula \(4 \times P(1 - P) / L^2\) (\(P = \) percentage of DR prevalence from previous studies). With an error of 10 %, the sample size was 96. (A total of 100 subjects were taken into account).

Statistical Analysis
The data obtained was statistically analyzed using analysis of variance (ANOVA) F test, Fischer's exact test, Bonferroni Test, Logistic regression, and linear regression analysis, using Epi info software version 7.2.2.6. A P - value less than 0.05 was accepted as statistically significant.

RESULTS
A total of 100 patients were recruited into this study, which was conducted over a span of 1 year, in the Department of Ophthalmology, S.V.R.R.G.G.H, Tirupati. In this study, the majority of patients were between 61-70 years of age, followed by 51 - 60 years of age. In total, 100 patients were included in the present study, 57 were male, and 43 were females. In the mild NPDR group, there were twelve males and eight females. In the moderate NPDR group, there were eleven males and nine females. In the severe NPDR group, there were ten males and eight females. In the very severe NPDR group, there were ten males and eight females. In the PDR group, there were fourteen males and ten females.

All the 100 patients included in the study were examined and categorized into various grades of diabetic retinopathy using EDTRS classification. They were categorically represented in Table 1. NPDR had the highest prevalence, amounting to 76 %, whereas PDR accounted for 24 % of the study population.

Range of HbA1c in various groups derived from the above table are:
- Mild NPDR the range of HbA1c was found from 6.4 % - 9.4 % with mean of 7.9 %
- Moderate NPDR the range was 6.8 % - 10.3 % with mean of 8.5 %
- Severe NPDR the range was 8.5 % – 11.3 % with mean of 9.9 %
- Very severe NPDR it was 10.2 % - 12.5 % with mean of 11.3 % and
- PDR the range was 10.5 % - 13.4 % with mean of 12 %

There was a statistically significant difference in results observed between the values of HbA1c and different grades of diabetic retinopathy with \(P = 0.021\). Mild and moderate NPDR was seen after a mean diabetic duration of 5.6 and 8.7 years, respectively. Severe NPDR, very severe NPDR, and PDR were seen after a mean diabetic duration of more than ten years. CSME was frequently seen in severe (29.4 %), very severe NPDR (35.3 %) groups and PDR (17.6 %) as compared to mild (0 %) and moderate NPDR (17.6 %). The relationship between the grades of DR and the duration of diabetes was found to be statistically significant. Similarly, CSME in more severe forms of retinopathy compared to milder forms was also found to be statistically significant.

Relationship between CSME and HbA1c Levels and Duration of Diabetes
The important analysis of CSME and its relationship with levels of HbA1c and duration of DM was studied in the study population of 100 patients, and the results obtained are represented in Table 4.

DISCUSSION
Accurate data concerning the type and severity of diabetic retinopathy and associated risk factors are of importance in planning a well-coordinated approach to the health problem posed by this complication of diabetes. Identifying the...
Duration of Diabetes and Severity of Diabetic Retinopathy

In the CURES Eye study,10 41.8 percent had DR after 15 years of diabetes, and the severity of DR proportionally increased with longer duration of diabetes. In addition, it has been demonstrated that for every five-year increase in the duration of diabetes, the risk for DR increased by 1.89 times. Similarly, in the Wisconsin epidemiologic study of diabetic retinopathy (WESDR),9 the widest and most prolonged population-based ophthalmologic survey reported that higher prevalence of DR was associated with longer duration of diabetes. Correlating with previous important studies related to this parameter, present study of 100 patients with DR on analysis showed a statistically significant association (P-value < 0.05) between the duration of DM and severity of DR, with patients having longer duration of DM (> 10 years) associated with either very severe NPDR or PDR and vice versa. This significant association might be explained by the fact that with prolonged duration of DM, there is increased risk of progression of micro vascular and macro vascular complications especially in those groups of patients who are having poor glycaemic control either due to non-adherence to drug therapy or inadequate drug dosages.

CSME and Relationship with HbA1c

Chou T. H et al.11 in their study stated that patients with HbA1c of 8.6 or above had higher prevalence of CSME. Strict sugar control decreased the risk of diabetic macular edema.
retinopathy. Diana et al. in 2005, conducted a study to assess the correlation between persistent diabetic macular oedema and HbA1c. They also concluded that persons with type 2 diabetes mellitus and persistent CSME have higher HbA1c at the time of diagnosis than patients with resolved CSME and those with bilateral disease have more elevated HbA1c than those with unilateral disease. Similar to above studies, the findings of our study suggested that higher the level of HbA1c in a patient, higher is the risk associated with the development of CSME (statistically significant with P-value of 0.007). Thus, decreasing HbA1c values or achieving ADA criteria can prevent or delay the onset/or progression of microvascular complications such as retinopathy. Because retinopathy is a serious microvascular complication, regular screening for diabetic retinopathy and tighter glycaemic control could reduce the number of people who develop vision-threatening retinopathy.

CSME and Relationship with Duration of Illness
Though previous studies showed there is significant relationship between the duration of illness (i.e. DM) and CSME, like Gaudric et al. our study didn't show any significant association between these variables (with P-value of 0.65). This non-significant finding in this study might be because of the small population size and single centre trial. Thus, decreasing the HbA1c value can prevent or delay the onset and/or progression of microvascular complications such as retinopathy. Therefore, regular screening of diabetic patients and tighter glycaemic control could reduce the number of people who develop vision-threatening retinopathy.

CONCLUSIONS
A statistically significant correlation was found between HbA1c levels and the severity of diabetic retinopathy, with more severe grades of diabetic retinopathy manifesting in patients with higher levels of HbA1c. Age of the patient, gender of the patient, hypertension, and modality of treatment did not have significant correlation when compared in different grades of diabetic retinopathy (P-value > 0.05). Reduction in the HbA1c concentration through strict glycaemic control in diabetic patients can reduce the severity of diabetic retinopathy.

Limitations
Information regarding the blood glucose levels, lipid profile, renal parameters in the patients, the psychosocial factors, including health care access and utilization, were not incorporated. These might modify the relationship between the known risk factors and the risk of developing DR.

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