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

Sidda Naik Bukke[1], Rama Lakshmi Badugu[2], Ramachandraiah Gurapa[3],
Sree Pushpa Vani Gopavaram[4], Rama Thulasi Bukkacherla[5]

[1, 2, 3, 4, 5] Department of Ophthalmology, S.V.R.R.G.G.H, Tirupati, Andhra Pradesh, India.

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

BACKGROUND

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.[1] 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.[2] 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. [3-5] 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 photocoagulation 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 ophthalmoscopy
- Indirect ophthalmoscopy
- 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.
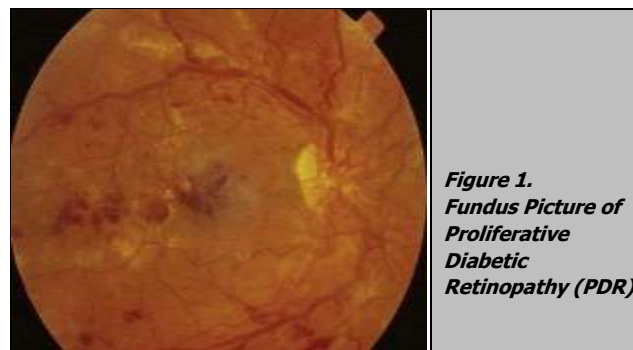
Figure 1. Fundus Picture of Proliferative Diabetic Retinopathy (PDR)

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 PQ 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 - value of 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.

Grades of DR	Number of Patients
Mild NPDR	20
Moderate NPDR	20
Severe NPDR	18
Very severe NPDR	18
PDR	24
Total	**100**

Table 1. Prevalence of Grades of Diabetic Retinopathy

Grades of DR	Number of Patients	Mean HbA1c	Std. Deviation
Mild	20	7.910	2.1982
Moderate	20	8.550	2.5172
Severe	18	9.944	1.8324
Very severe	18	11.356	1.4382
PDR	24	12.017	2.2819
Total	**100**	**10.010**	**2.5999**

Table 2. Relationship between Grades of Retinopathy and HbA1c Levels

Grades of DR	No. of Patients	Mean Duration	CSME
Mild	20	5.60	0 (0 %)
Moderate	20	8.70	6 (17.6 %)
Severe	18	13.56	10 (29.4 %)
Very severe	18	12.00	12 (35.3 %)
PDR	24	10.75	6 (17.6 %)
Total	**100**	**10.04**	**34**

Table 3. Relationship between Grades of DR and Duration of DM and CSME

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.

	Number	Mean Duration of Diabetes	Mean HbA1c
Patients with CSME	34	10.59	11.365
Patients without CSME	66	9.76	9.312

Table 4. Relationship between CSME and Diabetic Duration and HbA1c

The patients having CSME had higher HbA1c levels, whereas patients with no CSME had lower HbA1c levels, which was found to be statistically significant. (P = 0.007) Another parameter analyzed in the above table includes the association of CSME with the duration of diabetes, which didn't show any statistical significance (P - value = .601).

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

patient who may be at high risk of severe retinopathy is important in advising ophthalmic care. Such data is also helpful in planning future studies such as controlled clinical trials of the treatment of diabetes and diabetic retinopathy. This study was a descriptive correlative study done in 100 patients with diabetic retinopathy. 20 % of the patients manifested with mild NPDR, 20 % with moderate, and 18 % with severe NPDR. 18 % showed very severe NPDR, while the remaining 24 % had PDR. This study showed that age was not a statistically significant factor in the association with the severity of diabetic retinopathy, similar to a study conducted by Klein and Klein et al. noted that age had little significance in the progression of diabetic retinopathy, once the duration and type of retinopathy were considered.[6] In the majority of the prior studies in relation to diabetic retinopathy like Tapp et al.[7] there was no significant relationship between gender and DR. In the present study also, we found no significant association between the gender of the patient and severity of diabetic retinopathy (P - value : 0.583).

HbA1c Levels and Diabetic Retinopathy

In the past, many studies have highlighted and chalked out the cut offs for HbA1c levels in relation to the severity of DR. In 2013, Cho et al.[5] found that optimal cut off for detecting DR was 6.6 % and moderate to severe NPDR was 6.9 %, which was correlating with the present study where minimum cut off to detect diabetic retinopathy was noted as 6.6. Similarly, Zhang et al.[4] in 2016, in their study, showed that the prevalence of DR sharply increased when HbA1c exceeded 6.4 %, and their analysis showed that the optimal cut-off for detecting DR was 6.52 %, which was also correlating with the present study. One of the recent studies published in 2019 by Lind et al.[5] evaluated in 10,398 patients, stated that the risk of retinopathy was low if HbA1c levels were below 6.5 % and risk increased with higher HbA1c levels, thus highlighting the role of HbA1c in the clinical correlation of severity of DR. Reductions in blood glucose or HbA1c concentrations through tight blood glucose control in people with diabetes mellitus reduces the rate of progression microvascular complications such as DR, neuropathy, and nephropathy. In the present study, we found a cut off range of HbA1c for different grades of diabetic retinopathy above which retinopathy of that grade tended to manifest –

- Mild NPDR → 6.6 % - 9.4 %
- Moderate NPDR → 6.9 % -10.3 %
- Severe NPDR → 8.5 % – 11.3 %
- Very severe NPDR → 10.2 %-12.4 % and
- PDR →10.5 % - 13.4 %

Thus, correlating many studies done under this context, our study also highlighted the fact that the higher the level of HbA1c indicating poor glycaemic control, the more severe is the grade of DR in those set of patients.

Duration of Diabetes and Severity of Diabetic Retinopathy

In the CURES Eye study,[8] 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 group of patients who are having poor glycaemic control either due to non-adherence to drug therapy or inadequate drug dosages.

CSME and Severity of Diabetic Retinopathy

In one of the earliest studies by Gaudric et al. the incidence of diabetic maculopathy was 6 % among eyes with mild-moderate NPDR, 20 – 60 % among eyes with severe and very severe NPDR, and 70 - 74 % among eyes with PDR. Espiritu et al.[10] concluded in their study that the severity of retinopathy was significantly associated with maculopathy (P = 0.001). Even in the study by Kojima et al. (1990), there was a positive correlation between the level of concurrent retinopathy and maculopathy, where, besides retinal oedema, the macula showed other alterations in a higher percentage in PDR as compared to NPDR. In present study CSME was found in about 34 % (N = 34) of patients, in contrast to 66 % of patients who showed no evidence of diabetic maculopathy. However, on subset analysis we found that CSME was more frequently associated with very severe NPDR group of patients (34.4 %) followed by severe NPDR (29.3 %), and PDR and moderate NPDR group (17.6 % each) as compared to mild (0 %). Though our results showed high incidence of CSME in severe DR group of patients the incidence of the same was lower in PDR group of patients than in very severe NPDR group. These lower rates in PDR could have been due to the non-recognition of maculopathy in PDR due to retinal proliferation, vitreous haemorrhage, tractional bands, and other complications obscuring the macular region. We found a statistically significant correlation, which proved that the prevalence of CSME increased with increasing severity of diabetic retinopathy (P - value of 0.009).

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

retinopathy. Diana et al.[12] 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.

REFERENCES

[1] National society to prevent blindness. In: Visual problems in the US data analysis definition, data sources, detailed data tables, analysis, interpretation. New York: National society to prevent blindness 1980: p. 1-46.

[2] Koenig RJ, Peterson CM, Jones RL, et al. Correlation of glucose regulation and hemoglobin AIc in diabetes mellitus. N Engl J Med 1976;295(8):417-420.

[3] Cho N, Kim T, Woo S, et al. Optimal HbA1c cut-off for detecting diabetic retinopathy. Acta Diabetologica 2013;50(6):837-842.

[4] Zhang R, Li Y, Zhang S, et al. The association of retinopathy and plasma glucose and HbA1c: a validation of diabetes diagnostic criteria in a Chinese population. J Diabetes Res 2016;2016:4034129.

[5] Lind M, Pivodic A, Svensson A, et al. HbA1c level as a risk factor for retinopathy and nephropathy in children and adults with type 1 diabetes: Swedish population-based cohort study. BMJ 2019;366:l4894.

[6] Klein R, Klein BEK. Diabetic eye disease. Lancet 1997;350(9072):197-204.

[7] Tapp RJ, Shaw JE, Harper CA, et al. The prevalence of and factors associated with diabetic retinopathy in the Australian population. Diabetes Care 2003;26(6):1731-1737.

[8] Rema M, Ponnaiya M, Mohan V. Prevalence of retinopathy in non-insulin-dependent diabetes mellitus at a diabetes centre in southern India. Diabetes Res Clin Pract 1996;34(1):29-36.

[9] Klein R, Davis MD, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. A comparison of retinopathy in younger and older onset diabetic persons. Adv Exp Med Biol 1985;189:321-335.

[10] Espiritu R, Grace SY. Fluorescein angiographically evident diabetic maculopathy. Clinical Haemorrheology and Microcirculation 2003;29(3-4):357-365.

[11] Chou TH, Wu PC, Kuo JZ, et al. Relationship of diabetic macular edema with glycosylated haemoglobin. Eye (Lond) 2009;23(6):1360-1363.

[12] Diana VD, Syed MS, Jennifer US, et al. Persistent diabetic macular edema is associated with elevated HbA1c levels. American Journal Ophthalmol 2005;139(4):620-623.