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Clinical study on association of diabetic retinopathy severity with HbA1c level

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ABSTRACT

Background: Patients with diabetic retinopathy (DR) have a greater risk of blindness compared to those without diabetes. HbA1c is a valuable indicator used to assess the long-term management of diabetes mellitus. Hence, the main objective of this study was to explore the relationship between HbA1c levels and the severity of diabetic retinopathy.

Materials and Methods: This one-year prospective observational clinical study was conducted at the Department of Ophthalmology and Diabetic Clinic, Gandhi Medical College, Bhopal, involving 100 diabetic patients. Detailed medical histories related to their diabetes were recorded. The diabetic retinopathy status of each patient was assessed through a comprehensive ophthalmologic examination and classified according to the early treatment diabetic retinopathy study (ETDRS) system. Clinical data of the patients, including HbA1c levels, were gathered during the study period.

Results: Among the 100 patients, 29% were females, while the remaining 71% were males. A notable finding emerged, revealing a significant link between the severity of diabetic retinopathy and HbA1c levels. Additionally, the duration of diabetes and lipid levels also demonstrated a significant association with the severity of retinopathy (P value < 0.05). However, the age and gender of the patients did not exhibit a significant correlation when compared across different grades of diabetic retinopathy (P value > 0.05). ROC analysis revealed that an HbA1c cutoff of 7.6% was the most effective in detecting both the presence of any diabetic retinopathy and its grades.

Conclusions: A strong statistical relationship was found between HbA1c levels and the severity of diabetic retinopathy. Patients with higher HbA1c levels, indicating poorer blood sugar control, showed more severe grades of diabetic retinopathy. HbA1c levels emerged as a reliable predictor for both the presence and severity of diabetic retinopathy.

1. Introduction

Diabetes mellitus is a long-term metabolic condition characterized by elevated blood glucose levels caused by inadequate insulin production, insulin resistance, or a combination of both factors.[1] The global prevalence of diabetes mellitus is 9.3%, with approximately 463 million individuals affected. This number is projected to rise to 578 million (10.2%) by 2030. In India, the prevalence of diabetes is 8.9%.[1,2]

Typically, there exists a symptomless interval between the initial occurrence of high blood glucose levels and the clinical diagnosis, and this symptom-free phase is approximated to persist for 4-7 years. The prevalence is an estimate of the tip of iceberg, as there are many cases that go undiagnosed and untreated. Undiagnosed and untreated chronic hyperglycemia in newly diagnosed diabetes patients is associated with a higher incidence of microvascular

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complications. In certain instances, the initial symptoms may manifest as macrovascular complications of diabetes.[3] These complications include Diabetic Retinopathy, Diabetic Nephropathy, and Diabetic Neuropathy. In India, there is an increasing trend of newly diagnosed diabetes cases with the presence of these microvascular complications. Therefore, early detection and treatment of microvascular complications are crucial in preventing their progression, reducing morbidity and mortality among patients. By understanding the interrelationship between diabetes mellitus, its microvascular complications, and early detection, new preventive and therapeutic approaches can be developed to address these complications effectively.

As per the literature diabetic retinopathy common in newly detected diabetes mellitus patients.[3] The worldwide occurrence of diabetic retinopathy in individuals with diabetes stands at 22.27%, and within this prevalence, the proportion of sight-threatening diabetic retinopathy is 6.17%. For India specifically, the prevalence of diabetic retinopathy is reported to be 17.6%.[4] Its prevalence ranges from 35% -50% in cases with recently diagnosed DM type 2 in India.[4,5] It remains the most significant cause of blindness in most of the diabetic population. HbA1c level among DR subjects were found to be higher than without DR indicating that as HbA1c levels increase, DR prevalence also increases and there is a strong relationship between HbA1c levels and diabetes. Early detection and timely intervention can prevent the visual loss.[6]

Microvascular complications are primarily linked with poor glycaemic control. Role of other factors that can affect the onset and progression of these microvascular complications have also been studied like duration of DM, obesity, deranged lipid profile etc. Several studies[7,8] in the past had shown that HbA1c is a good indicator of long term control of blood glucose level in DM patients and could be correlated with severity of DM. The available literature on the correlation and impact of serum HbA1c levels in the development and progression of these microvascular complications is limited and lacks comprehensive data. Also, the interrelation amongst these 3 microvascular complications is not well established in Indian population.

Thus, the primary objective of this study was to investigate the association between serum HbA1c levels and the severity of microvascular complications, specifically diabetic retinopathy, in type II diabetic patients. By analyzing the clinical profile of diabetic retinopathy, we aimed to identify timely interventions that could prevent or mitigate the severity of sight-threatening and life-threatening complications associated with retinopathy.

2. Materials and Methods

This observational clinical study was conducted prospectively on patients diagnosed with type II diabetes mellitus. The study was carried out at the Department of Ophthalmology and Diabetic Clinic, Gandhi Medical College, Bhopal, Madhya Pradesh, India. Written and informed consent was obtained from all participants, and a thorough ocular examination and systemic history were taken, which included checking for any pre-existing non-diabetic retinopathy and maculopathy, non-diabetic renal disorder, previous laser photocoagulation therapy, and pre-existing neuropathy.

Ophthalmic evaluation comprises of measurement of best corrected visual acuity was recorded using Snellen chart for distant vision and near vision using Jaeger chat. A Goldman applanation tonometer was used to measure the intraocular pressure. Slit lamp bio microscopy was used to evaluate anterior segment. Pupils were dilated by instilling topical 2.5% phenylephrine and 0.5% tropicamide at an interval of 10-15 minutes, with punctal occlusion to avoid systemic absorption, dilated fundus examination was done with indirect ophthalmoscope using 20D lens. All the patients fulfilling inclusion criteria were subjected to following investigation, HbA1C level estimation by withdrawing three ml of blood sample of patient's peripheral vein collected and sent to the pathology laboratory. According to HbA1C level patient were grouped into Very good control (HbA1C<7), Good control (HbA1C between 7 and 8) and Poor control (HbA1C>8). All the data was recorded in a prescribed Performa and a master chart was prepared including all the cases recorded to analyze relationship between glycosylated hemoglobin and severity of Diabetic Retinopathy.

3. Results

Table 1 shows the distribution of study participants according to age, it was found that most of the study participants were in the age group of 41 - 60years (50%). Mean age of the study group was 51.46 ± 10.88 years. Most of the cases (48%) in the present study had history of DM for 5 – 10 years followed by 42% participants with 10-20 years of DM. The mean duration of DM in the study group was 12.29 ± 0.68 years. Out of 100 cases, 50% of the participants had HbA1c > 8% showing a poor glycaemic control, followed by 26% participants having HbA1c < 7% showing good glycaemic control and 24% participants had HbA1c level between 7 – 8% where glycaemic control was fair. Mean HbA1c level in the study group was 8.29 ± 1.71.

Figure 1 shows the severity of DR in the study group as per the modified ETDRS classification. It was found that 25% participants had no changes of diabetic retinopathy. In a group of NPDR 5% study participants had mild NPDR, 18% study participant had moderate NPDR and 16% study participants had severe NPDR. Severe PDR was seen in majority of cases 27% and 9% had moderate PDR. Table 2 shows comparison of CSME with PDR and NPDR. Out of total 39 study participants of NPDR 12 study participants were present with CSME. In cases of

Table 1: Demographic profile of study participants

Variable		No of Cases (N= 100)
	31 - 40 years	22
	41 - 50 years	30
Age	51 - 60 years	20
	61 - 70 years	24
	> 70 years	4
Gender	Male	71
	Female	29
Duration of DM	5-10 years	48
	10-20 years	42
	>20 years	10
Other Co-Morbidities	Hyperlipidaemia	76
	< 7 (good control)	26
HbA1c level	7 – 8 (fair control)	24
	> 8 (poor)	50

Table 2: Distribution of severity of DR according to CSME

Diabetic Retinopathy		With CSME	Without CSME	P Value
	No DR	0	0	
	NPDR	12	27	<0.0001
	PDR	30	6	
	Mild NPDR	0	5	
NPDR	Mod NPDR	2	16	<0.0001
	Severe NPDR	10	6	
PDR	Moderate PDR	3	6	<0.0001
	Severe PDR	27	0	
Hb1AC Level		7.92±1.67	9.34±1.42	0.0002

PDR, 30 study participants were present with CSME. The distribution of diabetic retinopathy severity based on the presence of clinically significant macular edema (CSME) was found to be statistically significant with a p-value of less than 0.05, indicating a strong correlation. In cases of NPDR, only 2 study participants of moderate NPDR were present with CSME and 16 were present without CSME. In cases of severe NPDR, 10 study participants were present with CSME and 6 were present without CSME. Out of the total 9 study participants of moderate PDR, 3 study participants were present with CSME and 6 were present without CSME. Out of total 27 study participants of severe PDR, all 27 study participants were present with CSME. The distribution of severity of DR according to CSME and mean HB1Ac levels between CSME and without CSME patients were observed to be statistically significant, showing the increased probability of developing CSME with increased severity of DR. Among study participants whose lies between 6-7 HbA1c levels most of them had no evidence diabetic retinopathy. Only few cases had mild to moderate NPDR, as glycaemic control deteriorated, there was increase in no. of cases and severity of diabetic retinopathy. The observed difference in HbA1c levels and the severity of diabetic retinopathy showed a strong statistical significance, with a p-value of less than 0.0001, confirming a clear direct relationship between HbA1c and the severity of diabetic retinopathy (Figure 2).

In the present study, HbA1c concentration was noticeably higher in the NPDR and PDR groups compared to the No DR group. The mean value of HbA1c in PDR group was 9.04±1.89, followed by NPDR group 8.40±1.07 and in No DR, group mean value of HbA1c was 6.75±0.51. The observed difference demonstrated a statistically significant result, as depicted in Figure 3.

On studying correlation of duration of DM and HbA1c level it was observed that those cases with longer duration of DM even with good to fair glycaemic control developed severe diabetic retinopathy when compared with those with lesser duration DM in same glycaemic control ($r = 0.51$; $P < 0.001$) (Figure 4). It was observed that there was random distribution of cases with diabetic retinopathy with age, however on statistical analysis it showed a very weak association ($p = 0.0510$) indicating that chances of diabetic retinopathy with same glycaemic control were higher with higher ages (Figure 5). Figure 6 displays the distribution of study participants based on the severity of DR concerning their HbA1c and cholesterol levels. Our analysis indicates that, despite similar glycaemic control, an increase in cholesterol level corresponds to an elevated likelihood of more severe DR (correlation coefficient, $r = 0.56$). This difference was found to be statistically significant, with a p-value of <0.0001, demonstrating a direct relationship between lipid profile and the severity of diabetic retinopathy, even at the same HbA1c level.

The ROC curve analysis revealed that the optimal HbA1c level for detecting any diabetic retinopathy was 7.6, demonstrating a sensitivity of 72% and specificity of 100%. Moreover, for identifying any moderate or severe retinopathy, the HbA1c level cutoff of 7.6 exhibited increased sensitivity (75.7%) and good specificity (96.7%). The overall discriminatory power, as determined by the AUC of HbA1c, was considered to be good and statistically significant for identifying both any diabetic retinopathy (AUC = 0.903 [95% CI, 0.846 to 0.960], p<0.0001) (Figure 7 A) and moderate/severe retinopathy (AUC = 0.912 [95% CI, 0.857 to 0.967], p<0.0001) (Figure 7 B).

4. Discussion

It is estimated that the prevalence of type 2 diabetes mellitus will double by the year 2030.[9] Diabetes is a medical condition that exhibits a strong association with a range of complications, encompassing both microvascular

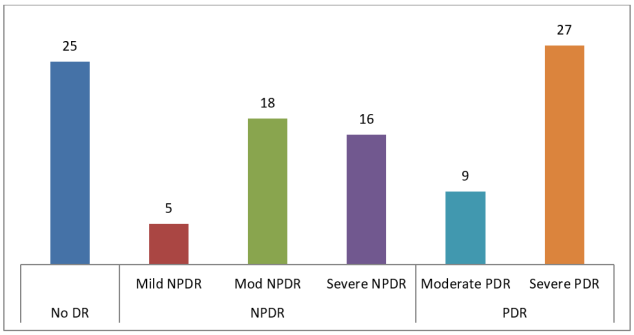

Figure 1: Distribution of participants according to Diabetic retinopathy- Fundus findings

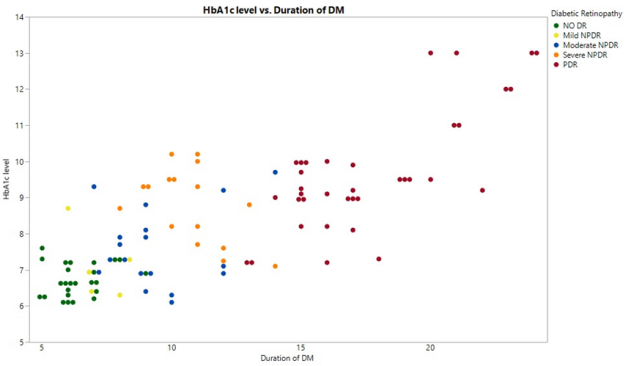

Figure 4: Scatter plot between duration of DM with HbA1c level with diabetic retinopathy

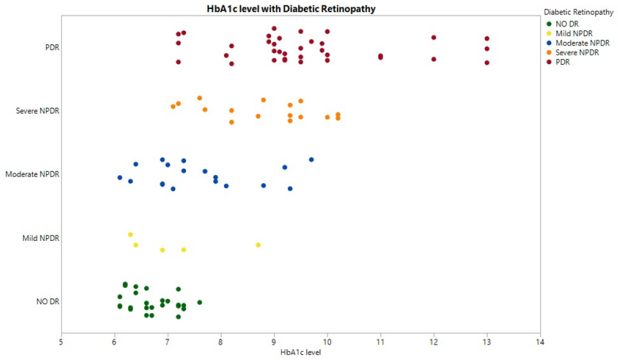

Figure 2: Scatter plot between HbA1c and diabetic retinopathy

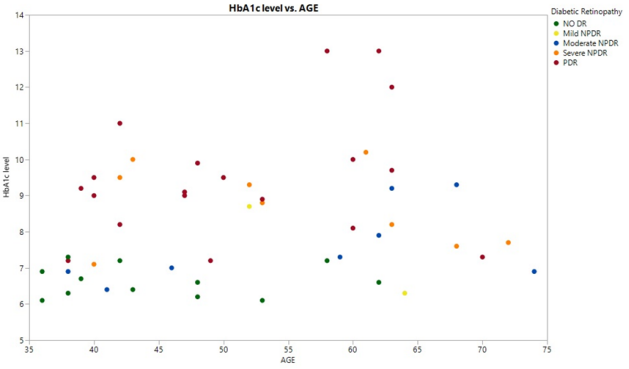

Figure 5: Scatter plot between age and HbA1c level with diabetic retinopathy

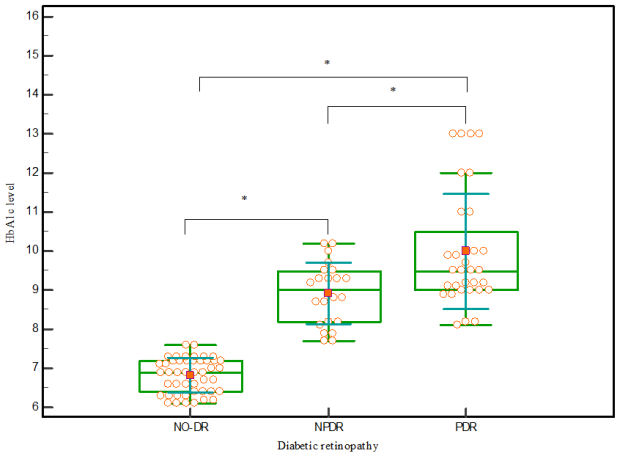

Figure 3: Comparison between HbA1c levels of diabetic retinopathy grades

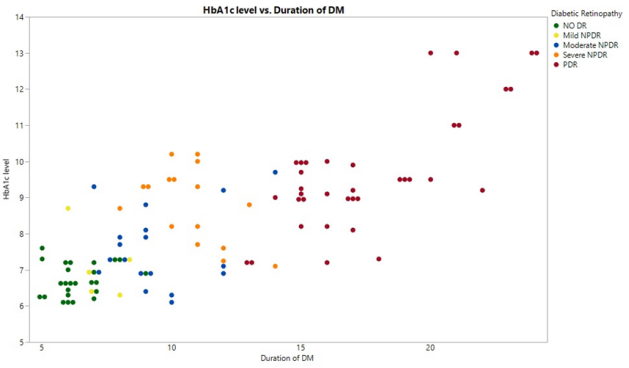

Figure 6: Scatter plot between lipid profile (LDL) and HbA1c level with diabetic retinopathy

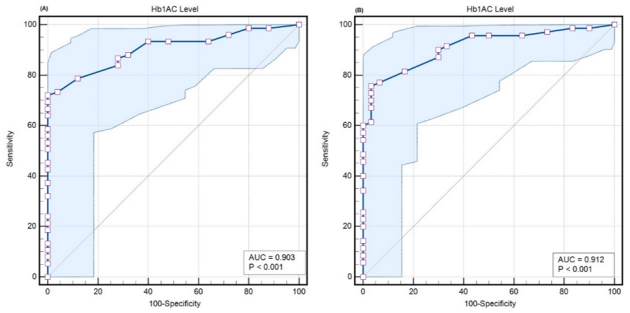

Figure 7: Receiver operating curves for an any diabetic retinopathy (**A**) and any moderate or severe diabetic retinopathy (**B**)

and macrovascular issues. The microvascular complications include retinopathy, nephropathy, and neuropathy, while the macrovascular complications consist of ischemic heart disease, peripheral vascular disease, and cerebrovascular disease. These complications can lead to damage in organs and tissues in about one third to one half of individuals diagnosed with diabetes.[10] Notably, among the microvascular complications, diabetic retinopathy stands as the most widespread, making a substantial contribution to the worldwide prevalence of blindness.[11]

In the present study male predilection was seen with 71% of males. Another study conducted by Niveditha H[12] with 50 study participants, out of which 31 participants were males and 19 study participants were females. Singh et al[13] in their study reported that 57.8% were males and 42.1% were females. Kumar et al[14] in their study reported that 55% were males and 45% were females. Santos et al.[15] in his study also reported similar findings. In a study conducted on the Indian population in 2016, it was found that the prevalence of diabetic retinopathy was significantly higher in men (68.5%) compared to women, and it was more prevalent in individuals aged between 50 to 70 years (75.5%).[16] Another study by Manaviat et al.[17] had a majority of female participants (58.64%) and the mean age of the patients was comparable to that in our present study (54.9 +/- 10.2 years). Conversely, the study by He et al.[18] had a majority of male patients (57%) with a mean age of 59.69 +/- 12.28 years. These findings suggest that the gender distribution of patients with diabetes and microalbuminuria may vary and is a characteristic specific to each study, rather than being a characteristic of the entire population.

In the current study, the largest proportion of study participants fell within the age range of 41-50 years, comprising 30% of the total. The average age of the study participants was determined to be 51.46 ± 10.88 years. As this study was conducted among type II DM which was seen in older individuals more commonly when compared to younger. Similar results were reported by Kumar et al[14] that majority of the participants in their study belonged to 50-60 years age group followed by 40–49 years. Eqbal et al.[19] reported in their study that most common age group was 51-60 years followed by 41-50 years. Similarly Singh et al[13] found in a study of 232 subjects with Diabetic Retinopathy, that most of the participants (69.1%) were in the age group of 51-65 years. Distribution of the study participant according to severity of diabetic retinopathy with HbA1c level and age (Figure 2). It was observed that there was random distribution of cases with diabetic retinopathy with age, however on statistical analysis it showed a weak association ($p = 0.0510$) indicating that chances of diabetic retinopathy with same glycaemic control were higher with higher ages.

In the present study, most of the study participants had 5–10 years history of DM (48%) followed by 42% study participants with 10-20 years history of DM, followed by 10% study participants had with duration of DM >20 years. Mean duration of disease was 12.29 ± 0 .68 years. In a study done by Niveditha et al[12] Mean duration of diabetes mellitus was 6.9 years. In the CURES Eye study,[20] DR affected 41.8% study participants after 15 years of diabetes, and the severity of DR increased proportionally with the duration diabetes. Additionally, research has shown that the risk for DR increased by 1.89 times for every additional five years duration of diabetes. Higher prevalence of DR was linked to longer duration of diabetes, which was also concluded by the Wisconsin Epidemiologic Study of DR (WESDR).[21] On studying correlation between duration of DM and HbA1c level it was observed that those cases with longer duration of DM even with good to fair glycaemic control developed severe diabetic retinopathy when compared with those with lesser duration of DM in same glycaemic control (Figure 3). Additionally, it was noted that the prevalence and severity of diabetic retinopathy showed a significant increase with longer duration of diabetes. This observation is consistent with the findings of various clinical and population studies[10,18,22–24] which have highlighted the heightened risk of diabetic retinopathy associated with early-onset diabetes (i.e., longer duration of diabetes).

In the present study, there were increased lipid profile associated with DR, it was found that 76% of patients had hyperlipidaemia. We observed moderate significantly associated correlation between DR and increased lipid profile ($r = 0.56$; $P < 0.001$). Hyperlipidemia, along with hyperglycemia and hypertension, is considered a major contributing factor to diabetic retinopathy.[25] Notably, there has been a significant correlation between elevated serum lipid levels and the presence of retinal hard exudates.[26] Shah et al[27] observed that 75% of the patients had abnormal lipid profiles, and this condition exhibited a significant association with diabetic retinopathy. Nevertheless, it is worth noting that a few studies have uncertain this association, though their numbers are limited.[28]

A common measure was taken to assess long-term glycaemic control as glycosylated haemoglobin (HbA1c). It was found that among study participants 25 were with No DR and had HbA1c level < 8% whereas 32 study participants had PDR with HbA1c level >8%. Among study participants whose HbA1c level lie between 6-7, most of them had no evidence of diabetic retinopathy. Only few cases had mild to moderate NPDR. As glycaemic control deteriorates, there was increase in no of cases and severity of diabetic retinopathy. This difference was statistically significant with p value <0.0001 showing direct relation of HbA1c with severity of diabetic retinopathy (Figure 3). Cho et al[29] reported mean HbA1c among their study participants were 8.29 ± 1.71. Out of total study participants 50% had HbA1c > 8%, followed by 26% participants having HbA1c < 7% and 24% participants having HbA1c between 7%-8%. In a study conducted by Klein et al.[30] showed that the risk of PDR was six times higher among diabetics with poor glycaemic control. In a study done by Niveditha et al[12] reported that NPDR was diagnosed in most of the participants, mild NPDR (28%), Severe NPDR (16%), and PDR (10%). HbA1c level was under very good control in 8% of study participants. There were 14% study participants had an HbA1c level that was under fair controlled (HbA1c between 6%-8%) and 78% of study participants had poorly controlled HbA1c (HbA1c > 8%). A study done by Sevak et al.[31] reported that most NPDR patients (28.58%) and No DR patients (60%) fell in the HbA1c level of <7%. More than 8% indicates poor control of HbA1c level, but 14.28% of diabetic patients without retinopathy had poor control of HbA1c. Diabetic retinopathy cases and controls exhibited a significant difference in HbA1c levels, with DR cases having a higher HbA1c than controls. They also reported that mean value of HbA1c in No DR was 6.56, in NPDR 7.21 and 7.91 in PDR group. These findings were concordant with our observations. Patel et al[7] with 120 study participants based study also find the significant correlation between HbA1c and grade of retinopathy. Therefore, as the severity of retinopathy increased, the mean HbA1c for the level of severity also increased. The UKPDS reported that degree of glycaemic control is the most important component for prevention of retinopathy.[32]

In this study, the majority of participants with diabetic retinopathy (DR) showed severe grades of DR when classified according to the presence of clinically significant macular edema (CSME). Conversely, a larger number of study participants had less severe grades of DR when CSME was not present. The distribution of DR severity based on CSME was found to be statistically significant. Saini et al[33] also reported in their study that the distribution of DR severity according to CSME was highly statistically significant. The concept of CSME holds importance as it represents the more severe end of the spectrum, often leading to visual impairment. Analyzing risk factors can help identify predisposing conditions and guide us toward appropriate treatments. Chou et al.[34] conducted a study where they found that patients with HbA1c levels of 8.6 or above had a higher prevalence of clinically significant macular edema (CSME). They concluded that strict control of blood sugar levels reduces the risk of diabetic macular retinopathy. Similarly, Do et al.,[35] investigated the correlation between persistent diabetic macular edema and HbA1c. They also found that individuals with type 2 diabetes mellitus and persistent CSME had higher HbA1c levels at the time of diagnosis compared to patients with resolved CSME. Additionally, patients with bilateral disease had higher HbA1c levels than those with unilateral disease. Our study's findings align with the above research, suggesting that higher HbA1c levels in a patient are associated with an increased risk of developing CSME (with a statistically significant P-value of 0.007). Thus, lowering HbA1c values or meeting the ADA criteria can potentially prevent or delay the onset or progression of microvascular complications like retinopathy.

In this study, an HbA1c cutoff of 7.6% demonstrated the most accurate detection of both any diabetic retinopathy and its grades. Our findings correlated well with Eqbal et al[19] who reported HbA1c level cut-off range between 6.3%-13.4% for any diabetic retinopathy. The findings of our study do not align with a study conducted in the south Asian population, which reported that the optimal HbA1c thresholds for detecting mild and moderate retinopathy were 6.6% and 7.0%, respectively. Furthermore, a consolidating findings of data between 1988 and 2004, suggested an optimal HbA1c cutoff of 6.4% to 6.5% for moderate or severe retinopathy.[36] The discrepancies observed in our study might be attributed to the relatively small sample size and our exclusive focus on diabetic cases.

5. Conclusion

In conclusion, the results from our study revealed a clear trend where an increase in HbA1c levels corresponded to a higher prevalence of diabetic retinopathy (DR), indicating a strong relationship between HbA1c levels and the severity of DR. Moreover, we observed a significant association between the duration of diabetes and lipid levels with the severity of DR. On the other hand, advanced age and gender exhibited a weaker correlation with DR severity. Based on our findings, an HbA1c cutoff of 7.6% was found to be the most effective in detecting both the presence of any diabetic retinopathy and moderate/severe retinopathy. However, it is crucial to exercise caution while utilizing this cutoff for diagnosing diabetes and detecting diabetic retinopathy, as other factors may also influence the disease's progression and presentation. Hence, comprehensive evaluation and careful consideration of multiple parameters are essential for accurate diagnosis and

management of diabetic retinopathy.

6. Source of Funding

None.

7. Conflict of Interest

None.

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