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A study of retinal changes in diabetes mellitus in association with glycosylated haemoglobin, haemoglobin and duration of diabetes mellitus in tertiary care teaching hospital

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Abstract
Introduction: Prevalence of diabetic retinopathy in India is 21.27%. Diabetic retinopathy was detected in 1.78% of the diabetic patients screened. Diabetic retinopathy is a major, potentially preventable, long term, microvascular complication of diabetes mellitus and a leading cause of visual disability and blindness in working-age population, which is the hallmark of generalized microangiopathy.
Materials and Methods: This is Cross Sectional Study Conducted Among Out Patients attending Ophthalmology OPD and Inpatients of tertiary care teaching hospital. Patients were enrolled for the study after obtaining written informed consent. Total 214 patients were screened in this study. Staging of Diabetic Retinopathy was done using Modified Arlie House classification.
Result: Amongst the total number of diabetic retinopathy patients, 138 (64.5%) patients were males and 76 (35.5%) patients were females. Out of the total number of females in the study 77.6% had diabetic retinopathy and amongst males 73.1% had diabetic retinopathy and severity of DR is more in males (10.9% versus 7.9%). There was no statistical significance seen with gender and diabetic retinopathy (chi square x2 =1.819, p=0.611). Retinopathy was seen in 74.8% of the subjects in study. Among them 37.9% were shown mild changes of DR and whereas 9.8% were having severe or very severe retinopathy. Median duration of diabetes is 2 years. Among them 15.9% were having diabetes for more than 10 years and 11.7% had from less than 1 year duration. Maximum number of people (35.5%) were having the duration of 1 - 5year.A positive co-orelation was observed between glycosylated haemoglobin and haemoglobin with severity of diabetic retinopathy.
Conclusion: Glycosylated Hemoglobin levels was significantly correlated to severity of diabetic retinopathy. Haemoglobin level have been significantly correlated to severity of diabetic retinopathy. Glucose control and anemia are identified to be important modifiable risk factors in diabetes mellitus patients. The presence of these risk factors should warn the ophthalmologists about the need to monitor the retina. Low haemoglobin level, which is common in patients from developing countries like India, needs to be detected and treated, thereby reducing the risk for developing DR.

Keywords: glycosylated haemoglobin, diabetic retinopathy, haemoglobin

Introduction

Diabetes mellitus prevalence was estimated to be 8.8% of the world's adult population and it is predicted to rise to 10.4% by 2040. Almost two third Type 2 and almost all Type 1 diabetics are expected to develop diabetic retinopathy over a period [1].

According to WHO, diabetic retinopathy is responsible for 3-7% of the total blindness in Asia [2].

Diabetic retinopathy prevalence in India is 21.27%. Diabetic retinopathy was detected in 1.78% of the diabetic patients screened [3].

As per world diabetes atlas 2017,425 million people have diabetes in world. India is projected to have around 72 million people with diabetes. The increase in prevalence has been rapid in urban areas and has been found to increase from 2% to 12% in span of 3 decades [4]. As per ICMR-INDIAB phase 1 final report, prevalence of the diabetes mellitus in India ranges from 10.9% to 14.25% in urban areas and 3% to 8.3% in rural areas [5]. There is also a growing concern that the region for diabetic epidemic would be South East Asian Region [6, 7].

Diabetic retinopathy is a major, potentially preventable, long term, microvascular complication of diabetes mellitus and a leading cause of visual disability and blindness in

working-age population, which is the hallmark of generalized microangiopathy [8].

While there are many risk factors which have been associated with the development and progression of diabetic retinopathy, the duration of the disease and the age of the patient are said to be the strongest predictors. Other risk factors like hypertension, pregnancy, blood glucose level control and presence of nephropathy are shown to have a strong association. Dyslipidaemia, microalbuminuria, BMI and smoking are some of the factors whose role as predictors of diabetic retinopathy is not well established [9, 10, 11]

Various factors are associated with the development and severity of DR including high blood pressure, proteinuria, duration of DM, administration of insulin and renal disease [13]. Glycated hemoglobin is the non-enzymatic addition of glucose to the N-terminal valine of the β chain of the hemoglobin molecule and is commonly known was HbA1c [14]. In 2010, HbA1c ≥6.5% was adopted by American Diabetes Association [15] and was subsequently World Health Organization (WHO) recommended for diagnosing diabetes [16]. HbA1c criteria for diagnosing diabetes was originated from the observations of several cross-sectional studies [17, 18, 19]. In this studies, the threshold of HbA1c was observed above the levels at which prevalence of DR, a specific complication representing the prognosis of diabetes, increased sharply. The progression rate of retinopathy is 37% less for each 1% decrease in HbA1c [20]. However, the specific glycaemic cut-off in association with different stages of DR is not studied in India. Presence of diabetic neuropathy, low serum albumin, younger age and low hematocrit were reported as risk factors for the development of more severe form of DR (high risk proliferative DR) and visual loss [21].

The present study is undertaken to determine the various fundus changes in diabetes mellitus in association of elevated levels of HbA1C and haemoglobin in absence of any renal abnormalities. The conflicting reports if any in the literature regarding the association and paucity of studies relative to the existing case load warrants this study.

Materials and Methods

This is a across sectional study conducted in Department of Ophthalmology among Out Patients and Inpatients of tertiary care teaching hospital. Patients were enrolled for the study after obtaining written informed consent. Total 214 patients were screened in this study.

Methods: After obtaining a written informed consent patients will be evaluated as follows

1) Detailed diabetic status of the patient

- Age of onset
- Duration of the disease
- Associated conditions like hypertension, renal, cardiovascular, cerebrovascular disease
- Any medications (Hypoglycemic drugs, Lipid lowering drugs)
- Family history
- Other risk factors like smoking, alcohol, tobacco use were recorded.

2) Detailed ophthalmic examination

- Best corrected visual acuity
- Refraction
- Slit lamp examination of Anterior Segment
- Dilated fundus evaluation with

- Direct ophthalmoscope
- Indirect ophthalmoscope
- Slit lamp bio microscopy using 90D or 78D lens
- Findings were recorded in Amsler chart

Staging of Diabetic Retinopathy was done using Modified Arlie House classification [13].

Inclusion criteria

1. Consented individual
2. OPD patients
3. In-Patients
4. Patients diagnosed to have diabetes mellitus.

Exclusion criteria

1. Patients with high myopia will be excluded from the study.
2. Patients with hazy ocular media in both the eyes and other retinal vascular disorders will be excluded from the study.

Statistical analysis

Collected data was analysed by both descriptive and inferential methods.

Descriptive methods such as mean and standard deviation were calculated for quantitative data, frequency and percentage were found out for categorical data.

Inferential methods such as chi square test was calculated to obtain the significance between the two parameters. ‘t’ test was used to compare various quantitative parameters between two categories.

ANOVA test and post hoc analysis was performed to obtain the significance across more than two categories.

SPSS analysis were performed using SPSS software 13 and ‘p’ value <0.05 is considered as significant.

Result

Table 1: Age Distribution

Age group in years	Frequency	Percentage (%)
<30	6	2.8
30-40	24	11.2
40 -50	39	18.2
50 -60	72	33.6
60 –70	52	24.3
70- 80	21	9.8
Total	214	100.0

The above table gives the age distribution across the 214 subjects. There were only 2.8% subjects who were below 30 years of age. 11.2% were between 31-40 years of age, 18.2% subjects were between 41 and 50 years of age, 33.6% subjects were between 51-60 years of age, 24.3% subjects were between 61-70 years of age and 9.8% above 70 years of age. The mean age of the group was 54.47±12.24.

Table 2: Diabetic Retinopathy with Age Distribution

		Age group in years						Total
		<30	30-40	40 -50	50 -60	60 --70	>70	
No evidence DR	Number of subjects	4	12	17	21	11	3	68
	Percentage	66.6%	50%	43.6%	29.2%	21.2%	14.2%	31.8%
Evidence of DR	Number of subjects	2	12	22	51	41	18	146
	Percentage	33.3%	50%	56.4%	70.8%	78.8%	85.8%	68.2%
Total	Number of subjects	6	24	39	72	52	21	214
	Percentage	2.8%	11.2%	18.2%	33.6%	24.3%	9.9%	100.0%

x2=13.936, p=0.016 ns

The above table shows a positive correlation with the presence of diabetic retinopathy with increasing age which was statistically significant (chi square x2=13.936, p=0.016).

Table 3: Diabetic Retinopathy With Gender Distribution

		Sex		Total
		Male	Female	
No evidence	Number of subjects	37	17	54
	Percentage	26.8%	22.4%	25.2%
Mild	Number of subjects	48	33	81
	Percentage	34.8%	43.4%	37.9%
Moderate	Number of subjects	38	20	58
	Percentage	27.5%	26.3%	27.1%
Severe	Number of subjects	15	6	21
	Percentage	10.9%	7.9%	9.8%
Total	Number of subjects	138	76	214
	Percentage	64.4%	35.6%	100.0%

X2=1.819 P=0.611 NS

Amongst the total number of diabetic retinopathy patients, 138 (64.5%) patients were males and 76 (35.5%) patients were females. Out of the total number of females in the study 77.6% had diabetic retinopathy and amongst males 73.1% had diabetic retinopathy and severity of DR is more in males (10.9% versus 7.9%). There was no statistical significance seen with gender and diabetic retinopathy (chi square x2 =1.819, p=0.611).

Table 4: The incidence of Retinopathy.

Presence and grading of DR	Frequency of DR	Percentage of DR (%)
No evidence	54	25.2
Mild	81	37.9
Moderate	58	27.1
Severe	18	8.4
Very severe	3	1.4
Total	214	100

Retinopathy was seen in 74.8% of the subjects studies. Among them 37.9% were shown mild changes of DR and whereas 9.8% were having severe or very severe retinopathy.

Table 5: Duration of Diabetes Mellitus with Retinopathy

Duration of diabetes in years	No of subjects	Percentage (%)
Below 1	13	11.1
1-5	25	35.5
6-10	76	30.8
Above 10	66	15.9
Newly detected	34	6.1
Total	214	100

Median duration of diabetes is 2 years. Among them 15.9% were having diabetes for more than 10 years and 11.1% had from less than 1 year duration. Maximum number of people (35.5%) were having the duration of 1 - 5year.

Table 6: Duration of Diabetes with Retinopathy

Diabetic Retinopathy		Duration of Diabetes mellitus					Total
		Newly detected	<1year	1-5year	6-10year	>10year	
No evidence DR	Number of subjects	7	10	28	8	1	54
	Percentage	53.8%	40.0%	36.8%	12.3%	2.9%	25.2%
Evidence DR	Number of subjects	6	15	48	58	8	160
	Percentage	46.2%	60.0%	63.2%	87.9%	97.1%	74.8%
Total	Number of subjects	13	25	76	66	34	214
	Percentage	100%	100%	100%	100%	100%	100%

X2=40.958 $p<0.001$ vhs

The association between the duration of diabetes with the retinopathy was found by using chi-square test. We could see that the retinopathy was found more in who were suffering from diabetes more than 10 years (97.1%%). Whereas even in the newly detected cases nearly 46.2% of them were having retinopathy. The association between these two factors were found to be significant ($p<0.001$).

Table 7: Comparison of Duration of Diabetes according to Retinopathy

	N[b]	Mean	Std. Deviation	F	P
No evidence	54	3.154	2.899		
Mild	81	6.289	5.194		
Moderate	58	7.965	5.947		
Severe	18	10.000	5.562		
Very severe	3	6.666	10.680	9.155	<0.001 vhs

Mean duration of Diabetes was estimated and it was found that as the mean duration of Diabetes increases the severity of retinopathy also increased. With no retinopathy the mean duration was found to 3.155 years, whereas duration more than 10years had severe retinopathy and the difference was found to be statistically significant (p<0.001).

Table 8: Comparison of Hba1c level with severity of diabetic retinopathy.

		N	Mean	Std. Deviation	H	p
Hba1c	No evidence	54	7.525	1.490		
	Mild	81	8.364	2.093		
	Moderate	58	8.605	1.657		
	Severe	18	10.026	1.985		
	Very severe	3	11.333	.551	45.994	<.001 vhs

Mean Hba1c levels increases with severity of DR changes. When there was no retinopathy the mean Hba1c level is less than 7.525.The mean HbA1c levels increases from 8.364 to 11.333 in mild change to severe changes of DR respectively. The above difference was found statistically significant (p<0.001)

Table 9: Comparison of mean Haemoglobin level with severity of Diabetic retinopathy.

		N	Mean	Std. Deviation	H	p
Hba1c	No evidence	54	7.525	1.490		
	Mild	81	8.364	2.093		
	Moderate	58	8.605	1.657		
	Severe	18	10.026	1.985		
	Very severe	3	11.333	.551	45.994	<.001 vhs

The Mean Haemoglobin level at different stages of Retinopathy was studied by applying ANOVA. It was seen that those who were not having retinopathy had haemoglobin value of 13.45gm% whereas with severe retinopathy the haemoglobin level decreases. In the mild group it was 11.94gm% and with severe it was 8.5%.The difference was found to be statistically significant (p<0.001)

Discussion

The age and gender distribution were fairly consistent with findings of other related studies [23]. It was found that majority of patients were in age group of 40-60 years with mean age 54.47 ± 12.24 years. Statistically significant correlation was found with increasing age and incidence of diabetic retinopathy (p=0.016). The relationship of retinopathy was in concordance to that found in other studies. APED study [24], CURES Eye Study [25], Dondana *et al*. [26] have also found significant correlation between the age and diabetic retinopathy.

In the current study 76 were females and 138 were males, which corresponds to 35.5% and 64.5% respectively, out of which 27.6% of females and 72.4% of the males had diabetic retinopathy. The prevalence of DR shown male predominance with male to female ratio was 2.6:1. In a clinical cohort of Chennai diabetic retinopathy appeared to be more prevalent in the males compared to females (sex ratio 2:1) [27]. Similar preponderance was seen in the CURES Eye study [28] and UKPDS study. However, the difference was not statistical significance with respect to the sex distribution in this study (p=0.529).

The prevalence of diabetic retinopathy increases with duration of diabetes. Patients with diabetes mellitus more than 10 years were 97% and below 1 year was 60%. The association of prevalence of diabetic retinopathy with duration diabetes mellitus was statistically significant (p<0.001). There may be some bias in estimating the real duration of diabetes in these patients, as the discovery could have been delayed due to lack of symptoms and the insidious onset of type 2 diabetes. Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) found that risk of retinopathy is directly related the duration of diabetes [29]. The CURES Eye study has found for every five-year increase in duration of diabetes, the risk for DR increased by 1.89 times [30].

The mean Hb with the retinopathy at different stages versus no evidence retinopathy was also studied. It was clearly seen that those who were not having retinopathy had normal hemoglobin whereas with changes of retinopathy, the mean hemoglobin level decreases progressively. The difference was found to be statistically significant (P<0.001)

Qiao *et al*. study showed that DM patients with hemoglobin level lower than 12 mg/dl were two times more likely to develop DR [31]. Davis *et al*. reported that low hematocrit is a risk factor for development and advancement of DR [32]. A similar risk of anemia with severe retinopathy was also reported in a case series by Shorb [33]. Irace *et al*. showed that the levels of blood viscosity, Hematocrit, and hemoglobin were lower in patients with DR compared with subjects without retinopathy [34].

In our study, mean HbA1c level was less when no evidence of retinopathy and severity of retinopathy increases as the level of mean HbA1c increases. The association of mean level of HbA1c with severity of diabetic retinopathy was statistically significant (P<0.001)

Results from the Diabetes Control and Complications Trial (DCCT) and the epidemiological data from the Wisconsin Epidemiological Study of DR (WESDR) have showed the strong relationship of glycemic control, development and progression of DR [35].

In study conducted by Australian Diabetes Society they reported that the patients with DR had a significant higher HbA1c levels [36].

In our study the association of prevalence of diabetic retinopathy with duration of diabetes mellitus was statistically significant. Decreased mean haemoglobin and increased mean Hba1c was associated with increased severity of diabetic retinopathy significantly.

Conclusion

Glycosylated Hemoglobin levels was also significantly correlated to severity of diabetic retinopathy. Haemoglobin level have been significantly correlated to severity of

diabetic retinopathy. Glucose control and anemia are identified to be important modifiable risk factors in diabetes mellitus patients. The presence these risk factors should warn the ophthalmologists about the need to monitor the retina. Low haemoglobin level, which is common in patients from developing countries like India, needs to be detected and treated, thereby reducing the risk for developing DR. Vision impairment could be prevented which is one of dreaded complications with early diagnosis and treatment.

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