

CORRELATION OF HBA1C WITH SIGHT-THREATENING DIABETIC RETINOPATHY (STDR) IN TYPE 2 DIABETES MELLITUS

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ABSTRACT

BACKGROUND

Diabetic retinopathy is a major cause of blindness in the world with India being set to emerge as the diabetic capital of the world. Visual disability from diabetes is a significant health problem, but its morbidity is largely preventable and treatable. HbA1c (glycosylated haemoglobin) is the best indicator of glycaemic control. It has long been known to predict the incidence and progression of diabetic retinopathy.

Our aim is to evaluate the correlation of STDR in type 2 diabetes mellitus with HbA1c levels.

MATERIALS AND METHODS

A cross-sectional study was carried out in the Department of Ophthalmology, Government Medical College, Kozhikode, among 250 randomly selected type 2 Diabetes Mellitus patients and they were grouped into STDR, non-STDR and no diabetic retinopathy based on ophthalmoscopy. HbA1c level was estimated and its correlation was analysed using SPSS software version 17.0. Association of STDR with duration of diabetes and Body Mass Index (BMI) were also studied.

RESULTS

Out of 250 patients studied, mean age was 58.98 with 126 males and 124 females and there was increased incidence of STDR in males. 104 patients with STDR had HbA1c value of more than 8, high incidence of STDR were noted with increasing levels of HbA1c and the correlation was statistically significant ($p = 0.02$). 74.1% of patients had STDR in the group with duration of diabetes 11 to 15 years, 90.90% in more than 21 years group compared to 43% in the 5 years group. Increase in duration of diabetes was found to be significantly associated with higher incidence of STDR ($p = 0.01$). Incidence of STDR were more in patients with normal BMI ($p = 0.03$).

CONCLUSION

Poor diabetic control as noted by high HbA1c level and longer duration of diabetes were significantly associated with sight-threatening diabetic retinopathy. Patients with STDR and high HbA1c levels have to be referred for appropriate evaluation and treatment at the earliest to prevent blindness.

KEYWORDS

Proliferative Diabetic Retinopathy, Sight-Threatening Diabetic Retinopathy (STDR), Glycosylated, Haemoglobin, HbA1c.

HOW TO CITE THIS ARTICLE: Kotancheri R, Ayoor AK, Syamanthakam A, et al. Correlation of HbA1C with Sight-Threatening Diabetic Retinopathy (STDR) in type 2 diabetes mellitus. J. Evid. Based Med. Healthc. 2017; 4(76), 4451-4455. DOI: 10.18410/jebmh/2017/887

BACKGROUND

Diabetes Mellitus (DM) is a metabolic disease characterised by hyperglycaemia resulting from defect in insulin secretion, insulin action or both. It is the most important disease, which can affect nearly every organ in the body leading to pathological and functional changes without

clinical symptoms and may be present for a long period of time before being detected. Type 2 diabetes is the commonest form. 4.8% of the 37 million cases of blindness throughout the world is attributable to Diabetic Retinopathy (DR). It was declared as the 5th leading cause of blindness by World Health Organisation and more than 90% of the cases can be prevented by early detection and treatment, of which tight glycaemic control is the most important measure.

Diabetic retinopathy is a microvascular complication of diabetes and it remains as a leading cause of legal blindness. It is the chronic progressive sight-threatening disease of retinal microvasculature. The most common early clinically visible manifestation includes microaneurysm formation and retinal haemorrhages. Glycaemic control is

Financial or Other, Competing Interest: None.

Submission 29-08-2017, Peer Review 04-09-2017,

Acceptance 18-09-2017, Published 19-09-2017.

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DOI: 10.18410/jebmh/2017/887



the key modifiable risk factor associated with development of diabetic retinopathy. Advanced glycation end products including glycosylated haemoglobin (HbA1c) are known to produce the microvascular complications in DR.

Duration of diabetes also correlated with increased severity of retinopathy from Nonproliferative Diabetic Retinopathy (NPDR) to Proliferative Diabetic Retinopathy (PDR). Early epidemiologic studies have showed a consistent relationship between glycated haemoglobin levels and incidence of diabetic retinopathy. By measuring glycated haemoglobin, we are able to get an overall picture of average blood sugar levels over a period of 2-3 months. HbA1c remains the only confirmed systemic prognostic biomarker of progression of DR.¹ In our scenario, studies highlighting the correlation HbA1c levels with sight-threatening diabetic retinopathy is lacking.

Body mass index is regarded as an indicator of metabolic control with obesity and overweight being risk factors for multiple diseases, its association with the progression of DR has to be analysed. Several studies showed no association between the two, while others demonstrated a significant decrease in incidence of diabetic retinopathy in higher body mass index.

The Early Treatment Diabetic Retinopathy Study (ETDRS) identified HbA1c as one of the most important risk factor for progression of retinopathy. Diabetes Control and Complications Trial (DCCT), the United Kingdom Prospective Diabetes Study (UKPDS)^{2,3} also evaluated the risk factors and incidence of DR.

Most of the studies have reported the association of HbA1c with different stages of diabetic retinopathy, the correlation of HbA1c with potentially sight-threatening diabetic retinopathy was not extensively studied. Sight-Threatening Diabetic Retinopathy (STDR) was defined as 'referable' retinopathy including severe NPDR, PDR or Clinically Significant Macular Oedema (CSME), and these are important causes for visual loss in diabetic population.

MATERIALS AND METHODS

This study was approved by the Institutional Ethics Committee of Government Medical College, Kozhikode.

Study Design: A cross-sectional study was done among 250 randomly selected type 2 diabetes mellitus patients.

Study Setting: The present study was conducted in the Department of Ophthalmology, Government Medical College, Kozhikode, during the period of one year from January to December 2012.

Study Population: Study population were type 2 diabetic patients satisfying the WHO criteria of diabetes. Patients attending the Outpatient Department of Ophthalmology and those referred from diabetic clinic run by the Department of General Medicine, Government Medical College, Kozhikode, were included in the study.

Study Variables included were:

1. HbA1c value.
2. Duration of diabetes.
3. Body Mass Index (BMI).

Inclusion Criteria: Patients diagnosed to have type 2 diabetes mellitus above 30 years of age.

Exclusion Criteria

1. Patients with other macular or retinal pathology.
2. History of significant ocular trauma.
3. Patients who underwent cataract surgery or laser treatment for diabetic retinopathy.
4. Patients with glaucoma, hazy media, known systemic disease which could manifest as retinal pathology.
5. Pregnant and lactating females.

Data Collection and Analysis

After obtaining written informed consent, detailed history including duration of diabetes, general and systemic examinations were performed. Comprehensive ocular examination, best corrected visual acuity, slit-lamp examination and intraocular pressure were recorded. Fundus examination of both eyes done with direct ophthalmoscope, indirect ophthalmoscope and slit-lamp with +90D Volk lens.

Retinopathy was graded according to ETDRS classification and the patients were grouped into three.

Group 0: No apparent diabetic retinopathy (no DR)

Group 1: Non-STDR (mild and moderate nonproliferative DR).

Group 2: STDR (severe NPDR, PDR and CSME).

STDR and non-STDR were grouped based on the fundus findings of severely affected eye and analysis done accordingly.

Visual acuity was categorised into 7 groups as follows. 6/6 - 0, 6/9 to 6/12 - 1, 6/18 to 6/60 - 2, 5/60 to 2/60 - 3, 1/60 to CFCF - 4, HM to PL - 5, No PL - 6. Analysis of DR with visual acuity was done in all cases.

Duration of diabetes in years was noted in all cases and grouped into 5 categories.

1. 0-5 years; 2. 6-10 years; 3. 11-15 years; 4. 16-20 years; 5. More than 21 years.

Correlation of duration of diabetes with sight-threatening DR was analysed.

Body Mass Index (BMI), the most commonly used index of body mass is calculated by dividing the weight in kilograms by the square of the height in meters. Body mass index was calculated in all the patients and they were grouped into 4 categories- 1. Less than 18.5; 2. 18.5-23.99; 3. 24 - 29.99, 4. More than 30. Association of BMI with sight-threatening diabetic retinopathy was analysed.

Blood and urine routine, FBS, PPBS, RFT, serum cholesterol and HbA1c were estimated.

HbA1c was measured by High Performance Liquid Chromatography (HPLC) technique from the Department of Pathology. The American Cardiology Association referred values for HbA1c were categorised into four groups.

- 0. Less than 6.
- 1. 6.1 - 7 (well controlled).
- 2. 7.1 - 8 (fair control).
- 3. More than 8 (poor control).

The collected data were analysed by using SPSS software version-17.0. Chi-square test was used to compare the variables.

RESULTS

We studied a total of 250 patients with a mean age of 58.98 (range 31 to 84 years), gender distribution being 126 males and 124 females.

Out of 126 male patients, 70 of them had STDR, while out of 124 female patients, only 63 of them had STDR suggesting increased incidence of STDR in male patients.

Gender	STDR	Non-STDR	Total
Male	70	56	126
Female	63	61	124
Total	133	117	250

Table 1. Number of STDR and Non-STDR

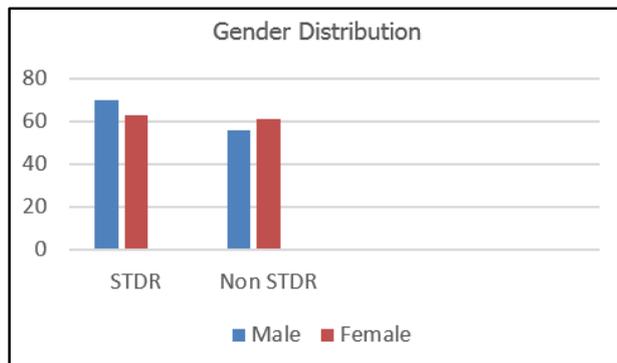


Figure 1. Gender Distribution

Glycosylated HbA1c levels of all the 250 patients were compared with the presence or absence of STDR. Out of 250 patients, 49 patients had HbA1c <6. Among those 49 patients, 22 patients had no DR, 13 patients had mild-to-moderate NPDR (non-STDR), 14 patients had STDR.

There were a total of 46 patients with HbA1c 6.1 to 7 out of this 20 patients had no DR, 8 patients had mild-to-moderate retinopathy (non-STDR) and 18 patients had STDR.

Out of 51 patients with HbA1c 7.1-8, 11 patients had no DR, 14 patients had mild-to-moderate NPDR with no STDR and 26 patients had STDR. 104 patients had HbA1c level >8, out of which, 11 patients had no DR, 18 patients had mild-to-moderate NPDR (Non-STDR) and 75 patients had STDR. We also found that out of 155 patients with HbA1c >7, 101 patients had STDR.

Out of 133 patients with STDR, 101 patients had HbA1c >7. There was an increase in the incidence of STDR with increasing range of HbA1c and this was statistically significant with a 'p' value of 0.02.

HbA1c	No DR	Non-STDR	STDR	Total
Less than 6	22 44.9%	13 26.5%	14 28.6%	49 100%
6.1 - 7	20 43.5%	8 17.4%	18 39.1%	46 100%
7.1 - 8	11 21.6%	14 27.5%	26 51%	51 100%
>8	11 10.6%	18 17.3%	75 72.1%	104 100%
Total	64 25.6%	53 21.2%	133 53.2%	250 100.0%

Table 2. Relation between HbA1c and STDR

Duration of diabetes was correlated with presence or absence of STDR. Out of 250 patients, 43% had STDR with duration of diabetes between 0-5 years, 52.3% had STDR with 6 - 10 years of duration, 52% patients had STDR, 55.3% patients had STDR with 11-15 years of diabetes and 74.1% patient had STDR with a duration of diabetes of 16-20 years. Of the patients with more than 21 years of duration of diabetes, 90.90% had STDR. It revealed an increase in incidence of STDR with increasing duration of diabetes and there was statistically significant correlation with a 'p' value of 0.01.

Duration Years	No DR	Non-STDR	STDR	Total
0 - 5	44 44%	13 13%	43 43%	100 100%
6 - 10	11 16.9%	20 30.8%	34 52.3%	65 100%
11 - 15	9 19.1%	12 25.6%	26 55.3%	47 100%
16 - 20	0 0	7 25.9%	20 74.1%	27 100%
>21	0 0	1 9.1%	10 90.9%	11 100%
Total	64 25.6%	53 21.2%	133 53.2%	250 100%

Table 3. Relation between Duration of Diabetes and STDR

The correlation of body mass index with the STDR was analysed and the results were as follows. Out of 48 patients with BMI <18.5, 52% had STDR. Among 161 patients, i.e. majority of the study group with BMI 18.5-23.99, 55.9% had STDR. Of the total 33 patients with BMI 24-29.99, 48.5% had STDR. 75% of patients with BMI >30 had no DR and only 25% had STDR. Based on this study compared with normal weight, overweight was associated with reduced risk of development of STDR and underweight with increased risk of STDR (p value 0.03).

BMI	No DR	Non-STDR	STDR	Total
Less than 18.5	11 22.9%	12 25.0%	25 52.1%	48 100%
18.5-23.99	35 21.7%	36 22.4%	90 55.9%	161 100%
24-29.99	12 36.4%	5 15.2%	16 48.5%	33 100%
>30	6 75%	0 0	2 25%	8 100%

Table 4. Relation between BMI and STDR

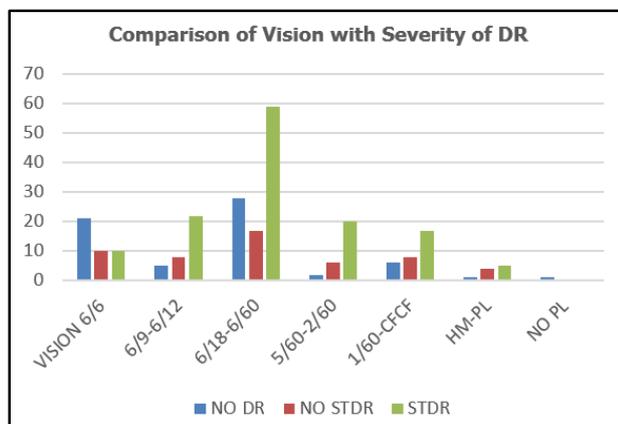


Figure 2. Comparison of Vision with Severity of DR

From the figure 2, it is observed that majority of the patients' vision were in the range of 6/18-6/60 and those with severe vision loss belonged to sight-threatening retinopathy group.

DISCUSSION

The testing of HbA1c is very important in the diagnosis and management of DR, also in the progression of disease. The inclusion of HbA1c in the screening protocols has gained significant importance not only in the diagnosis and management of DM, but also in the onset and progression of DR. Glycation of tissue protein is a well-known pathophysiological mechanism in the complications related to diabetes leading to the formation of advanced glycation end-products (HbA1c). Tight glycaemic control as measured by these factors is strongly associated with a decreased prevalence of microvascular complications related to DM like retinopathy.

DCCT⁴ showed 76% reduction in the rate of development of any retinopathy and an 80% reduction in the progression of established retinopathy in patients with strict control of diabetes. 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.⁵ In the CURES eye study for every 2% elevation of HbA1c, the risk of diabetic retinopathy increases by a factor of 1.7.^{6,7} In UKPDS,⁴ the risk reduction in eye complications for every 1% decrease in HbA1c was 19%.

In a population-based study on 5999 patients conducted by Rajiv Raman et al at Sankara Nethralaya, Chennai, HbA1c was found to be significantly associated with STDR and non-STDR group as compared to the no diabetic retinopathy group.⁸ Our results also comparable with this study as there was increasing incidence of STDR with increasing range of HbA1c. But, they categorised STDR and non-STDR group as per the fundus photographs taken as a part of screening programme of general population.

Rajendra Prasad et al observed in their study that there was an increase in the severity of retinopathy with higher levels of HbA1c.⁹ Our study also showed similar results and we could also specifically postulate the correlation with vision-threatening diabetic retinopathy with HbA1c levels.

They have not studied the correlation with sight-threatening diabetic retinopathy.

Duration of DM, an important predictor of DR determines the exposure time of other risk factors. Al-Sarraf¹⁰ et al noticed that patients with 10 to 19 years of disease are twice as likely to have DR and approximately 3 times more when the exposure is more than 20 years. According to a recent study conducted in USA each year of DM represents a 6% increase in chance of DR. This correlation with duration of diabetes was first demonstrated in the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) with a higher prevalence in 25, 60 and 80% for 5, 10 and 15 years of evolution of DM, respectively.⁵ In addition to afore mentioned, several other studies showed statistical significance for this factor both in type 1 and type 2 DM, perhaps the most important independent risk factor for DR.^{11,12,13,14}

In this study, we got the results suggesting that there was an increase in incidence of STDR with increasing duration of diabetes.

Several studies showed no association between BMI and DR and other positive association. Ahmed et al in a follow up of involving 977 type 2 DM during 5, 10 and 15 years, did not find an increased risk of DR in any of the categories studied.¹⁵ Yoshida et al presented statistical significance in DR frequencies in patients with BMI >23.7 kg/m² only after 7 years of follow up.¹⁶ In this study, normal BMI is associated with increased risk of STDR followed by low BMI and high BMI is associated with low risk of development of STDR.

Even though, this study showed neither being overweight nor obesity is associated with STDR, it is well proven that obesity is a risk factor for diabetes mellitus, and hence it must be emphasised that maintaining a healthy body weight is essential to avoid further multisystem damage.

Thus, it can be inferred from this study that higher HbA1c values have a positive association with the development of STDR, which is related to the duration of diabetes, so estimation of HbA1c should be made mandatory as a part of diabetic retinopathy evaluation.

CONCLUSION

There was increasing incidence of sight-threatening diabetic retinopathy with increasing range of HbA1c. Hence, poor control of diabetes is a major risk factor for developing sight-threatening diabetic retinopathy. Duration of diabetes is also significantly associated with the presence of STDR in type 2 DM. We also found that overweight and obesity is associated with a reduced risk of development of STDR.

Hence, good glycaemic control right from the time of diagnosis of diabetes is beneficial in preventing the onset and progression of retinopathy. Targeting HbA1c level of less than 7% is recommended for slowing down the progression of diabetic retinopathy. Patients with sight-threatening diabetic retinopathy may have relatively good vision in spite of progressive pathological changes in the

retina and those with high HbA1c levels of more than 7% have to be referred for appropriate evaluation and treatment at the earliest to prevent blindness.

Limitations

This cross-sectional study was limited to the data available in the hospital and not obtained prospectively. Comparisons cannot be made with community-based studies.

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