Original article:

Study of correlation of blood levels of haemoglobin A1c to the presence of diabetic retinopathy in patients with type II Diabetes Mellitus

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Abstract:
Introduction: Diabetes mellitus (DM) is reaching epidemic proportions in the world today and it is by far the most prevalent endocrine disease. Glycosylated haemoglobin (HbA1c) serves as an integrator of the mean blood glucose over several preceding weeks. Hemoglobin undergoes nonenzymatic glycosylation in the presence of plasma glucose.

Materials and methods: This cross-sectional study was comprised of all the patients of DR attending the OPD, in-patients & referrals to ophthalmology department at Rohilkhand Medical College & Hospital. Inclusion criteria was Participants diagnosed to have type II DM with retinopathy changes in the fundus were included in this study.

Results: the mean HbA1c of cases with CSME was 9.92 ± 1.32 and that of cases without CSME was 8.46 ± 1.46. Comparison of the means of HbA1c in patients with and without CSME revealed statistically significant association of CSME with HbA1c.

Conclusion: The poor metabolic control as demonstrated by high HbA1c is significantly associated with severity of retinopathy and presence of CSME. From the analysis of our study, we recommend to maintain HbA1c levels below 7.2% which may reduce the risk of development and progression of diabetic retinopathy.

Keywords: Diabetes mellitus, retinopathy

INTRODUCTION
Diabetes mellitus (DM) is reaching epidemic proportions in the world today and it is by far the most prevalent endocrine disease. Glycosylated haemoglobin (HbA1c) serves as an integrator of the mean blood glucose over several preceding weeks. Hemoglobin undergoes nonenzymatic glycosylation in the presence of plasma glucose. 1 Normal levels of glucose produce a normal amount of glycated hemoglobin. As the average amount of plasma glucose increases, the fraction of glycated hemoglobin increases in a predictable way. This serves as a marker for average blood glucose levels over the previous months prior to the measurement. Normally 5% of total hemoglobin is glycosylated. The HbA1c is formed slowly and continuously during the 120 day life span of the erythrocyte. The cumulative amount of HbA1c is proportional to the average glucose concentration to which the erythrocyte is exposed. In poorly controlled diabetes, diabetics have mean HbA1c level 50% higher than normal. 2 Decrease in glycosylated haemoglobin levels is associated with a significant decrease in the progression of DR.
Nowadays, monitoring HbA1c levels is the gold standard for assessing average blood glucose concentration over past three months (3,4). The target level of HbA1c which is needed for adequate glycemic control in DM is unknown. The aim of the present study is to assess the relationship between HbA1c levels and DR in the patients with type 2 DM and to correlate the levels of severity of retinopathy with levels of HbA1c.

With this view present study was planned to determine the correlation of blood levels of haemoglobin A1c to the presence of diabetic retinopathy in patients with type II Diabetes Mellitus (DM).

MATERIALS AND METHODS
This cross-sectional study was comprised of all the patients of DR attending the OPD, in-patients & referrals to ophthalmology department at Rohilkhand Medical College & Hospital.

Inclusion criteria:
1. Participants diagnosed to have type II DM with retinopathy changes in the fundus were included in this study.

Exclusion criteria:
1. Participants with very hazy ocular media (i.e. ocular fundus not clearly visible by indirect ophthalmoscopy) were excluded from the study.
2. Participants who did not accept the informed consent
3. Pregnant women

After taking informed consent, all patients were examined according to a predesigned proforma. Relevant history regarding the diabetes with respect to age of onset, duration, nature, and effect of treatment received was also taken.

A general physical examination was performed followed by a complete ophthalmic examination, a detailed fundus evaluation was performed using a direct ophthalmoscopy, indirect ophthalmoscopy along with slit lamp bimicroscopy with +90 D lens. All the findings were documented in the Performa and verified by the guide.

All patients were subjected to seven field fundus photography. Fundus Fluorescein Angiography was performed only when clinically necessary.

Laboratory investigations done:
1. FBS levels
2. Glycosylated haemoglobin (HbA1c) levels to determine the glycemic control

Examination of HbA1c:
Glycosylated haemoglobin was measured by Immunoturbidimetric method using Quantia HbA1c which is a turbidimetric immunoassay for the direct determination of HbA1c in human blood without the need to estimate total haemoglobin. It is expressed in %.

Data obtained was analyzed using SPSS version 12.0 of computer analysis.

OBSERVATIONS AND RESULTS
There were 59 males and 41 females in our study group, revealing a male preponderance in our recruited study population. The male: female ratio was 1.43:1.

The present study constituted 17% mild NPDR, 48% moderate NPDR, 22% severe NPDR, 8% early PDR and 5% of high risk PDR. Out of 100 retinopathy patients studied moderate NPDR accounted for nearly half the patients while the other half consisted of early PDR, mild and severe NPDR.
Out of the 100 cases of diabetic retinopathy, 22% had CSME, 17% in NPDR and 5% in PDR.

Age at diagnosis was calculated as patient’s age at point of examination minus duration of diabetes. The above table shows that around 11 of 17 (65%) cases with 41-50 years age group, 34 out of 48 (71%) of moderate NPDR patients were in 41-50 years age group, 15 out of 22 cases (68%) patients with severe NPDR. This revealed that as the age at diagnosis of diabetes increases, severity of retinopathy increases. The age at diagnosis was significantly associated with the severity of retinopathy.

<table>
<thead>
<tr>
<th>Retinopathy severity</th>
<th>MEAN</th>
<th>S.D.</th>
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<tbody>
<tr>
<td>Mild NPDR</td>
<td>7.82</td>
<td>1.35</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>8.46</td>
<td>1.34</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>9.96</td>
<td>1.51</td>
</tr>
<tr>
<td>Early PDR</td>
<td>9.13</td>
<td>1.48</td>
</tr>
<tr>
<td>High Risk PDR</td>
<td>9.28</td>
<td>1.13</td>
</tr>
</tbody>
</table>

Table 1. Association of HbA1c with severity of retinopathy: Mean and standard deviation (S.D) of HbA1c in retinopathy:

The table shows the means of HbA1c in each level of severity of diabetic retinopathy. The mean of HbA1c in mild NPDR was 7.82 ± 1.35, in moderate NPDR was 8.46 ± 1.34, in severe NPDR was 9.96 ± 1.51, in Early PDR was 9.13 ± 1.48 and in High risk PDR was 9.28 ± 1.13. Therefore, as the severity of retinopathy increased, the mean HbA1c for that level of severity also increased, the standard deviation (S.D) in each group being small.

<table>
<thead>
<tr>
<th>PRESENCE OR ABSENCE OF CSME</th>
</tr>
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<tbody>
<tr>
<td>RETINOPATHY</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>CSME PRESENT</td>
</tr>
<tr>
<td>CSME ABSENT</td>
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</tbody>
</table>

*P value by Students unpaired t-test is p<0.0001 (HS)*
The above table shows that the mean HbA1c of cases with CSME was 9.92 ± 1.32 and that of cases without CSME was 8.46 ± 1.46. Comparison of the means of HbA1c in patients with and without CSME revealed statistically significant association of CSME with HbA1c.

Table 3. Association of FBS with CSME:

<table>
<thead>
<tr>
<th>PRESENCE OR ABSENCE OF CSME</th>
<th>FBS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEAN</td>
<td>S.D.</td>
</tr>
<tr>
<td>CSME PRESENT</td>
<td>185.18</td>
<td>50.7</td>
</tr>
<tr>
<td>CSME ABSENT</td>
<td>161.12</td>
<td>47.98</td>
</tr>
</tbody>
</table>

\[ P=0.0429 \text{(significant)} \]

This table shows that the mean FBS of cases with CSME was 185.18 ± 50.7 and that of cases without CSME was 161.12 ± 47.98. Comparison of the means of FBS in patients with and without CSME revealed statistically significant association between CSME and FBS.

DISCUSSION

This study included 100 patients. The mean age of participants in the study was 57.19±7.09 and the Male: Female ratio is 1.43:1. The mean age of onset of 100 participants was 44.72 ± 7.36. Mean duration of diabetes was 12.47 ± 5.92. The mean glycosylated Hemoglobin in the study population was 8.78 ± 1.54.

It has also been seen in an earlier Indian study that the mean age diagnosis or onset was 46.5 ± 10.25 years and the mean duration of diabetes was 7.6 ± 5 years. The UKPDS revealed a mean HbA1c of 8.6%, the values ranging from 5.3% to 15.6%. These findings are close to the findings of our study. There were 59 males and 41 females in our study group, with a male: female ratio of 1.43:1. Similar results of DR prevalence being more in males were depicted in WESDR study. Contrary to this, Bajpai et al revealed higher female preponderance, the analysis showed that there was no significant variation in the stages of retinopathy based on sex of the patient.

The present study included 100 cases of retinopathy which constituted 17% mild NPDR, 48% moderate NPDR, 22% severe NPDR, 8% PDR and 5% high risk PDR. The Early Treatment Diabetic Retinopathy Study identified the HbA1C as one of the most important risk factors for the prognosis to high risk proliferative retinopathy. The Diabetes Control and Complication Trial results were
stratified by HbA1c levels, there was a 35% to 40% reduction in the risk of retinopathy progression for every 10% decrease in HbA1c (e.g. from 8% to 7.2%), indicating a fivefold increase in the risk for patients with HbA1c of about 10% versus those with 7%.

Epidemiologic analysis of the UKPDS data showed a continuous relationship between the risk of microvascular complications and glycemia, so for every percentage point decrease in HbA1C (e.g. 9% to 8%), there was a 35% reduction in the risk of microvascular complications. And a clear relationship was seen between the increasing HbA1c values and increasing proportion of patients with non-sight threatening diabetic retinopathy and sight threatening diabetic retinopathy (p <0.0001) in a study done on 1414 subjects in Chennai in 2010 which also gave a targeted value of HbA1c as >8% (which would give maximum yield of sight threatening diabetic retinopathy. The WESDR also found that HbA1c correlated with a consistent increase in retinopathy from the lowest (5.4- 8.5%) to the highest quartile (11.6-20.8%).

Similarly, in our study, the mean values of HbA1c in non-proliferative levels of diabetic retinopathy have indisputable difference. The S.D. of each level being considerably small, made the difference more relevant.

In this study, the glycemic status of the patients was studied by measuring HbA1c levels. When the HbA1c values were compared in the groups with increasing severity of retinopathy, increasing levels of HbA1c were noted showing a significant correlation. There were 76% of mild NPDR cases, 73% of moderate NPDR cases and 27% of severe NPDR cases in 6.5% -8.5% range of HbA1c. Whereas in HbA1c range 8.6%-10.5%, mild & moderate NPDR cases reduced to 24% and 21% respectively and severe NPDR cases increased to 45%. And high-risk PDR raised from 20% to 60% when HbA1c raises from 6.5%-8.5% range to 8.6%-10.5%. This revealed an increasing trend of severity of retinopathy with raise in HbA1c. Therefore, it was noted that poor glycemic control, indicated by high HbA1c levels, led to the worsening of the retinopathy. Mean value of HbA1c was found to be higher in proliferative retinopathy in study done in 1991.

Some reports showed that the prevalence of DR significantly increased at a HbA1c value between 6.0% and 7% (94). Later, a value of 6.5% was seen to be a cut-off which could detect at least moderate retinopathy. As seen in this study, the severity of retinopathy increased, the mean FBS for the level of severity also increased. The standard deviation (S.D) in each group being considerably large.

Distribution of FBS along the severity of retinopathy revealed homogeneity among all groups and thus the association was found to be statistically non-significant.

In our study, the comparison of the means of HbA1c in patients with and without CSME revealed statistically significant association of CSME with HbA1c.

CONCLUSION

The poor metabolic control as demonstrated by high HbA1c is significantly associated with severity of retinopathy and presence of CSME. From the analysis of our study, we recommend to maintain HbA1c levels below 7.2% which may reduce the risk of development and progression of diabetic retinopathy.
REFERENCES:


