Role of Glycosylated Haemoglobin in Microvascular Complications in Type 2 Diabetes Mellitus

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ABSTRACT

Background: Diabetes mellitus is one of the most common chronic diseases in nearly all countries, and continues to increase in numbers and significance, as changing lifestyles lead to reduced physical activity, and increased obesity.

Materials and Methods: The study included 100 type 2 diabetes mellitus patients. The patients were divided into 2 groups of 50 each. In group 1, cases were type 2 diabetic patients without microvascular complications and in group 2, type 2 diabetic patients were with microvascular complications. These patients underwent various clinical tests like Urine analysis (for evaluation of U. Albumin), blood sampling (for complete haemogram, plasma glucose, HbA1c, Renal function tests).

Results: Mean Fasting, post-prandial blood sugar level, HbA1c, Urine albumin, blood urea and serum creatinine among test group was significantly more than control group. Among test group, 48 patients had nephropathy, 19 patients had neuropathy and 34 patients had retinopathy.

Conclusion: HbA1c provides a reliable measure of chronic glycaemia and correlates well with the risk of long term diabetic complications so that it is currently considered the test of choice for monitoring and chronic management of diabetes. However, the cut point of HbA1c from the diagnostic point of view is still controversial.

Key words: Macroalbuminuria, Microalbuminuria, Nephropathy, Neuropathy, Retinopathy.

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INTRODUCTION

Diabetes mellitus is a global epidemic that is projected to rise to 7.7% (438million) in 2030.1 It is a life-long debilitating disease, the complications of which are not only by the duration of diabetes but also by the average level of chronic glycaemia2,3, which is measured most reliably with glycated hemoglobin assay. In normoglycemic subjects a small proportion of hemoglobin A is attached to a carbohydrate moiety thus creating what is called glycated haemoglobin.4 In conditions of sustained hyperglycemia, such as in diabetes mellitus, the proportion of hemoglobin that is glycated is increased substantially.4,5 A linear relationship between microvascular complications and duration of disease was established by the authors where they documented the presence of microvasculopathy across different age groups in their study in 25-40% of diabetic patients aged >25 years with more than 5 years duration of diabetes. Researchers such as Krentz et al. and Al-Wakeel et al. have observed that both microvascular and macrovascular complications develop simultaneously in diabetes.6,7 The studies conducted by Armetz et al.8 and Kilpatrick et al.9 in diabetic patients have shown a significant positive correlation b/w HbA1c and age as well as duration of diabetes.

In contradiction to this Kabadi10 found no significant relationship between age, duration of diabetes and fasting blood glucose (FBG), glycated hemoglobin, glycated protein or glycated albumin. According to the results of many longitudinal and cross-sectional studies it has been demonstrated that the earliest detectable abnormality in NIDDM is impairment in the body's ability to respond to insulin.11

One of the study in which newly diagnosed type 2 diabetes have been studied have shown that insulin sensitivity correlated inversely with fasting insulin and the insulin level increased with the duration of diabetes.12 The United Kingdom Prospective Diabetes Study (UKPDS) has also confirmed the relation between glycaemic control and the development of microangiopathy in Type II (non-insulin-dependent) diabetic patients and has also documented the aggravating role of increased bloodpressure.13,14 Several large clinical trials have demonstrated that tight blood glucose control correlates with a reduction in the microvascular complications of diabetes.15

The American Diabetes Association (ADA) has designated HbA1C level of <7 % as a goal of optimal blood glucose control16 and the
American Association of clinical endocrinologists has further recommended HbA1C levels of <6.5%.\(^\text{17}\) While it has not always been clear that aggressive glycemic control can reduce the end-organ complications of diabetes,\(^\text{18}\) recent evidence indicates that aggressive glycemic control in type 2 diabetes is associated with a 25% lower incidence of microvascular end points.\(^\text{19}\)

It is obvious that information on prevalence of type 2 diabetes mellitus related complications is important for the adjustment of policies and practices in diabetic care management to gain better control of type 2 diabetes mellitus. Thus, the present study was conducted to assess the significance of HbA1c in micro-vascular complications occurring in type 2 DM.

MATERIALS AND METHODS

The present cross-sectional study was carried out in TMMC and RC, Moradabad from the period January 2016 to December 2016, which included Type 2 diabetes mellitus patients who attended the diabetes clinic and were admitted to the medicine ward.

Study Population

The study included 100 type 2 diabetes mellitus patients and divided into 2 groups of 50 each. Group 1 consisted of 50 diabetes mellitus patients without any microvascular complications and Group 2 consisted of 50 diabetes mellitus patients with any microvascular complications. The following inclusion / and exclusion criteria were used:

Inclusion Criteria

- Only Type 2 diabetes patients in the age group 35 – 69 years with any microvascular complications for 1 year.

Exclusion Criteria

- No previous h/o any systemic condition related to peripheral neuropathy (Malnutrition, alcoholic neuropathy).
- Any neuromuscular diagnosis such as myopathy, familial polyneuropathy, Chronic polyneuropathy, GB syndrome.
- Any known visual disturbance diagnosed due to retinal problem.
- Neuropathy or nephropathy associated with exogenous toxins, metals or drugs.
- Pregnancy and post-menopausal women with HRT.

Data Collection

The basic general information of the study population was as follows: Name, Age, Gender, and Dietary habits. The medical history of the study population included: Duration of Diabetes, past medical History, Family History, Smoking Status, Alcohol intake and Drug History.

These patients underwent various clinical tests like Urine analysis (for evaluation of U. Albumin), blood sampling (for complete haemogram, plasma glucose, HbA1c, Renal function tests). Blood samples were collected by venipuncture after ensuring 8 hours of overnight fasting. Blood samples were taken in EDTA disodium coated and plain vials and centrifuged to obtain plasma and serum; and accordingly Biochemistry analysis was carried out.

The biochemical investigations included: HbA1c (done suing the Cobas HbA1c Test), Fasting blood glucose and Post-prandial blood glucose (GOD – POD method). The kidney function tests included Urine (Routine and Microscopic Examination), 24 hours urinary protein (Quantitative determination of albumin in human urine by turbidometric Immunoassay), Blood Urea (GLDH – UREASE method) and Serum Creatinine (Modified Jaffe’s Kinetic Method) for detecting Nephropathy

Statistical Analysis

Data was tabulated as Mean ± S.D. Results were analysed using non-parametric test (Chi square and Mann Whitney U test) and parametric test (t-test).The correlation between 2 numerical variables was done using Pearson correlation coefficient analysis. P value of less than 0.05 was considered to be statistically significant.

RESULTS

In this study in the control group 68% patients were male and 32% were females. In the test group 64% patients were male and 36% patients were female. The mean age of the control group was 53.44 ±11.64 years and test group was 59.46± 9.30 years and mean weight of control group was 63.44±8.86 kgs and of test group was 76.84±7.39 kgs. The mean BMI of control group was 26.35±4.72 kg/m² and test group was 31.10±5.76 kg/m² and mean duration of diabetes among control group was 3.39±1.14 years and test group was 11.7 ±2.22 years.

Mean Fasting and post-prandial blood sugar level among test group (291.02±38.04 and 323.46±40.12 mg/100ml respectively) was significantly higher than control group (187.9±36.49 and 219.34±38.86 mg/100ml respectively). Mean HbA1c among test group (11.68 ±1.29%) was significantly more than control group(8.26 ±1.09%). (Table 1)

Mean Urine albumin, blood urea and serum creatinine among test group (501.16±457.73* mg/24 hrs, 74.28±48.51 mg/dl and 2.49±1.45 mg/100ml respectively) was significantly more than control group(22.12±4.70 mg/24 hrs, 15.34 ± 3.02 mg/dl and 0.78± 0.15 mg/100ml respectively). (Table 1)

Among control group, there was a significant correlation of glycosylated haemoglobin with age, weight, Body Mass Index, FBS and PPBS. Among Test group, there was a significant correlation of glycosylated haemoglobin with age, duration of diabetes, Fasting blood glucose, postprandial blood glucose, Urine albumin and Blood urea. (Table 2)

<table>
<thead>
<tr>
<th>Table 1: Biochemical characteristics of patients in both groups (Mean±SD)</th>
</tr>
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<tbody>
<tr>
<td><strong>Parameter</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Fasting Blood Glucose (FBS) (mg/100ml)</td>
</tr>
<tr>
<td>Post Prandial Blood Glucose (PPBS) (mg/100ml)</td>
</tr>
<tr>
<td>Glycosylated Hemoglobin (HbA1c) (%)</td>
</tr>
<tr>
<td>Urine Albumin (mg/m/24 hr)</td>
</tr>
<tr>
<td>Blood Urea (mg/dl)</td>
</tr>
<tr>
<td>Serum Creatinine (mg/100ml)</td>
</tr>
</tbody>
</table>

Unpaired "t"-test  Mann-Whitney U test * Significant difference
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Table 2: Correlation of Glycosylated Hemoglobin with demographic and biochemical parameters in control and test groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group</th>
<th>Test group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r value</td>
<td>p value</td>
</tr>
<tr>
<td>Age</td>
<td>0.48</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Height</td>
<td>-0.08</td>
<td>0.57</td>
</tr>
<tr>
<td>Weight</td>
<td>0.39</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Body Mass Index (B.M.I)</td>
<td>0.38</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>-0.18</td>
<td>0.22</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>0.22</td>
<td>0.13</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>0.07</td>
<td>0.62</td>
</tr>
<tr>
<td>Duration of Diabetes</td>
<td>0.15</td>
<td>0.30</td>
</tr>
<tr>
<td>Fasting Blood Glucose (FBS) (mg/100ml)</td>
<td>0.89</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Post Prandial Blood Glucose (PPBS) (mg/100ml)</td>
<td>0.72</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Urine Albumin (mg/24 hr)</td>
<td>0.17</td>
<td>0.25</td>
</tr>
<tr>
<td>Blood Urea (mg/dl)</td>
<td>0.17</td>
<td>0.23</td>
</tr>
<tr>
<td>Serum Creatinine (mg/100ml)</td>
<td>-0.24</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Pearson’s correlation test

* Significant difference

DISCUSSION

In present study, test group had higher mean age, weight, BMI and longer duration of diabetes as compared to the Control Group. This showed the correlation of age with incidence of microangiopathy in diabetics demonstrating a positive relationship between the two variables. This study is comparable to EURODIAB, IDDM complication study which showed significant trends in the prevalence of microvascular complications with increasing age and duration of diabetes. However Saltykov et al found that patient’s age did not significantly affect the frequency and degree of diabetic microangiopathy. Hashimoto et al also showed that duration of diabetes was more prolonged in cases of diabetics with microangiopathies as compared to the duration in group of patients without microangiopathies.

In the present study, Fastig Blood glucose, post-prandial blood Glucose, HbA1c, Urine albumin, Blood Urea and Serum creatinine levels are more among Diabetics with microangiopathies than in diabetics without microangiopathies. This reflects that poor glycemic control is a risk factor that causes microvascular complications. In patients with T2DM the risk of diabetic complications is strongly associated with hyperglycemia. Each 1% reduction in HbA1c was associated with 37% decrease in risk for microvascular complications and 2% decrease in risk in the of any end point or death related to diabetes.

Both Fasting blood sugar and postprandial blood sugar levels were found to be higher in test group compared to control group. Yamini et al also showed statistically significant differences with the mean FBS levels and PPBS levels in diabetics without complications and diabetics with complications. HbA1c levels were found to be higher in test group than control group in the current study reflecting that increased HbA1c level is an indicator of assessing the severity of microangiopathies in diabetics.

Diabetics having higher HbA1c level are more prone to develop microangiopathies.

In our study, Urine albumin, Blood urea and Serum creatinine levels were found to be more among patients with microalbuminuria. Poorly controlled blood sugar levels can lead to increase in the serum urea levels and thus increase the chances of patients suffering from diabetic nephropathy.

In the present study, significant correlation of HbA1c level has been observed with age, weight and BMI. Contrasting to this, Weiner et al did not observe any significant correlation of HbA1c with age and stated that therefore age specific reference ranges for HbA1c were not required. Hashimoto et al in his study found that HbA1c increased with age which might be due to aging process itself. Furthermore, both BMI and hereditary predispose to diabetes but not active participation in sports affects this age dependent increase in HbA1c levels.

In the present study, significant correlation of glycosylated haemoglobin was seen with age and duration of diabetes. With advancement in age and duration of diabetes, there is gradual tendency for the level of blood sugar to raise along with a subsequent increase in HbA1c. In various studies, HbA1c levels demonstrated a significant increase with duration of diabetes. Variables like age at onset of disease, duration of disease and age of patients, influence glycemia directly and HbA1c indirectly.

In the present study, among test group, glycosylated haemoglobin showed significant correlation with Fasting blood sugar, Post-prandial blood sugar, and Urine albumin and blood urea. Belay et al showed that PPBS has a closer association with HbA1c than FBS; hence PPBS is better in predicting over all glycemic control in the absence of HbA1c.

Monitoring of PPBS is more helpful to achieving optimal glycemic control and prevent long term diabetes complications than FBS alone in absence of HbA1c especially in developing countries.

This correlation proved that longer duration of exposure of RBCs to hyperglycemia has direct relationship with HbA1c levels. This indicates that HbA1c can be used as a predictor for nephropathy.

CONCLUSION

There is positive direct correlation between increasing age of diabetics and incidence of microangiopathy. HbA1c provided a reliable measure of chronic glycemia and correlates well with the risk of long term diabetic complications so that it is currently...
considered the test of choice for monitoring and chronic management of diabetes. However, the cut point of HbA1c from the diagnostic point of view is still controversial. Thus since HbA1c level is proportional to average blood glucose concentration over the previous four weeks to three months and is not influenced by the recent physical and/or emotional fluctuations. It gives an idea of glycemic status of diabetic patients for 3 months duration.

REFERENCES

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