Incidence and Association of Glycated Hemoglobin Levels with Iron Deficiency Anemia in Patients with or without Diabetes – A Study in a Semi Urban Area

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Abstract
Introduction: HbA1c and other hemoglobinins constitute the HbA1 fraction of the adult HbA3. HbA1c is also affected by pregnancy5,6, uremia7, hemolytic anemia8, hemoglobinopathies9, acute and chronic blood loss10,11, Vitamin B12, folate deficiencies. Iron deficiency anemia is also shown to have a considerable effect on HbA1c levels12. Studies have shown that reduced iron levels are correlated with increased levels of HbA1c leading to false high levels of HbA1c in individuals.

Materials and Methods: 1000 patients each with and without diabetes were included into the study. Hemoglobin levels, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), hematocrit, platelet count, total blood picture, differential leucocyte count was done for all samples. Samples from patients with IDA were tested for all the above parameters at base line, after 1 week, 1 month and 2 months following iron treatment. Type of anemia was categorized and mild moderate and severe based on hemoglobin levels.

Results: Preponderance of females were seen in the anemic cases over males. 11.1% of non-diabetic and 16.3% of the diabetic patients were anemic. The prevalence of low hemoglobin and low iron content was seen in 2.8% of the cases among non-diabetics while low Hb and normal iron levels were seen among 4.6% of the cases. Normal Hb with iron deficiency were seen among 3.7% of the cases while among the diabetics it was 2.1%, 7.3% and 6.9% respectively. Mean hemoglobin levels of all the severe anemic patients at base line was 5.9 ± 1.2, 9.1 ± 0.9 after 1 month and 10.6 ± 1.5 after 2 months of treatment.

Conclusion: There is a significant association of HbA1c levels and Iron Deficiency Anemia according to our study, though more studies need to be conducted to assess a proper clinical diagnosis

Keywords: Iron Deficiency anemia, HbA1c, glycated hemoglobin, diabetic patients, non-diabetic patients

Introduction
HbA1c is formed by the glycation of the terminal valine of the β-chain of hemoglobin. It is used as an indicator of patients glycemic status over the past 3 months2,3. HbA1c and other hemoglobinins constitute the HbA1 fraction of the adult HbA3. A1c is the most common fraction found in the HbA1 fractions. HbA1c should be present below 7% in all diabetic patients according to the American Diabetes Association, so as to prevent the development of micro vascular complications4. Apart from being affected by the blood glucose levels, HbA1c is also affected by pregnancy5,6, uremia7, hemolytic anemia8, hemoglobinopathies9, acute and chronic blood loss10,11, Vitamin B12, folate deficiencies. Iron deficiency anemia is also shown to have a considerable effect on HbA1c levels12.

Iron deficiency is one of the most prevalent type of malnutrition. Ferritin is the form in which iron is stored, and testing amount of ferritin reflects the iron status. Globally, 50% of anemia is attributed to iron deficiency13. Studies have shown that reduced iron levels are correlated with increased levels of HbA1c leading to false high levels of HbA1c in non-diabetic individuals14. Though one of the most common cause of nutritional deficiency, there have been many reports of inconsistency in HbA1c levels and the clinical implications12,14.

We have therefore conducted this study to investigate the effects of Iron deficiency anemia on HbA1c levels in diabetic and non-diabetic patients.

Material and Methods
This retrospective study was conducted in the department of Biochemistry at ACSR Government Medical College over a period of two years.1000 diabetic patients and 1000 non diabetic patients aged between 18 – 70 years with or without anemia who underwent hemoglobin concentration and HbA1c level testing were taken into consideration. All female patients of child bearing age, who had amenorrhea were screened for pregnancy and were excluded from the study if found positive. Patients were screened for disorders like hemolytic anemias, hemoglobinopathies, and uremia with high creatinine and urea levels and were also excluded if found positive.
Written informed consent was taken from all patients. Detailed history was taken and physical examination was done for all patients. Hemoglobin levels, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MHCH), mean corpuscular volume (MCV), hematocrit, platelet count, total blood picture, differential leucocyte count was done for all samples. Samples from patients with IDA were tested for all the above parameters at base line, after 1 week, 1 month and 2 months following iron treatment.

The anemia type was defined by peripheral smear examination. The type of anemia was divided into mild, moderate and severe based on the hemoglobin levels. Mild anemia was categorized as hemoglobin levels of 12 – 12.9 g/dL in males and 11-11.9 g/dL in females; moderate anemia with 9-11.9 g/dL in males and 8-10.9 in females ; severe was <9g/dl in males and <8 g/dL in females. Patients with microcytic (MCV <80fL) or hypochromic (MCH < 26 pg/cell) indices were considered as iron deficient anemia (IDA). IDA was confirmed by serum ferritin levels < 29 ng/ml in males and <10 ng/ml in females. The tests for these levels was redone after 1 month and 2 month.

Results

Out of total 2000 patients, 64% were females and 36% were males in the diabetic group and 68% females and 32% males in the non-diabetic group (Fig: 1). In the control group, 60% were females and 40% were males. The mean age for the patient group was 32.7±1.8 while that of control group was 33.2±1.4.

Among the non-diabetic patients, 111(11.1%) of them were anemic, with 95(85.6%) of them severely anemic, 15(13.5%) moderately anemic and only 1(1%) had mild anemia. This was probably due to the fact that persons with mild anemia were not normally sent for HbA1c testing. 163(16.3%) of the diabetic patients, who underwent HbA1c testing were anemic. Of these, 117(71.8%) were having severe anemia, 44(27%) were with moderate anemia. (Fig: 2). There were no cases of mild anemia among the diabetic patients.
The most common symptom observed was weakness and pallor in 100% of the anemic cases and malaise in 96%. 46% of the patients had no energy or interest in work and dyspnea was seen in 42% of the cases. Splenomegaly was seen in 12% of the cases and systolic murmur in 50% of the patients (fig: 3).

The prevalence of low hemoglobin and low iron content was seen in 2.8% of the cases among non-diabetics while low Hb and normal iron levels were seen among 4.6% of the cases. Normal Hb with iron deficiency were seen among 3.7% of the cases while among the diabetics it was 2.1%, 7.3% and 6.9% respectively. (Table: 1)

<table>
<thead>
<tr>
<th></th>
<th>Diabetic N=1000</th>
<th>Non Diabetic N=1000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females (%)</td>
<td>Males (%)</td>
</tr>
<tr>
<td></td>
<td>(n = 642)</td>
<td>(n = 358)</td>
</tr>
<tr>
<td>Low Hb, low iron</td>
<td>16 (2.5%)</td>
<td>5 (1.4%)</td>
</tr>
<tr>
<td>Low Hb, Normal iron</td>
<td>54 (8.4%)</td>
<td>19 (5.3%)</td>
</tr>
<tr>
<td>Normal Hb, low iron</td>
<td>47 (7.3%)</td>
<td>22 (6.1%)</td>
</tr>
<tr>
<td>Normal Hb, Normal iron</td>
<td>525 (81.8%)</td>
<td>312 (87.2%)</td>
</tr>
</tbody>
</table>

Females were predominantly affected with anemia, both iron deficiency and non-iron deficiency type than males.

Mean hemoglobin levels of all the severe anemic patients at base line was 5.9 ± 1.2, 9.1 ± 0.9 after 1 month and 10.6 ± 1.5 after 2 months of treatment. The mean hemoglobin level of the normal patients (Normal Hb and normal iron content) it was 12.6 ± 3.8. It was observed that though treatment with iron supplements were given to the patients for 3 months, the iron content was still lower than that of normal non anemic patients

Table 2: Ferritin, hemoglobin and HbA1c levels in IDA patients before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>Patients at baseline</th>
<th>Patients at 1 month</th>
<th>Patients at 2 months</th>
<th>Normal patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Ferritin level (ng/ml)</td>
<td>17.7 ± 5.8</td>
<td>145.6 ± 67.1</td>
<td>256 ± 65.2</td>
<td>235.0 ± 35.5</td>
</tr>
<tr>
<td>Hemoglobin level (g/dL)</td>
<td>5.9 ± 1.2</td>
<td>9.1 ± 0.9</td>
<td>10.6 ± 1.5</td>
<td>12.6 ± 3.8</td>
</tr>
<tr>
<td>HbA1c levels (%)</td>
<td>6.3 ± 0.3</td>
<td>5.4 ± 0.7</td>
<td>5.1 ± 0.4</td>
<td>5.6 ± 0.5</td>
</tr>
</tbody>
</table>

Among the diabetics whose fasting blood sugar levels was <100mg/dL, the mean Hb levels was found to be 10.1 ± 1.9 in males and 9.4 ± 2.3 in females. Mean HbA1c value was found to be 6.14 ± 1.1% among the moderate anemia cases while it was 5.5 ± 1.3 among the severe anemia patients.
Discussion

Iron deficiency anemia is one of the most common types of anemia. HbA1c is a glycated hemoglobin that is used to determine the glycemic status of a patient for the past 3 months. But there are a few conditions which also affect the levels of HbA1c like pregnancy, uremia, hemolytic anemias, hemoglobinopathies, acute and chronic blood loss.8-11

Our study shows that Iron deficiency anemia is more common among women than men. This was observed in a similar study by Nitin Sinha et al who reported females to be more affected with IDA than males.

Our results show that there is a positive correlation between hemoglobin and HbA1c concentrations. HbA1c levels tend to be higher in cases of iron deficiency. On treatment with iron supplements, the HbA1c levels decrease. This was observed first by Brooks et al who reported that HbA1c levels in 35 non diabetic patients with IDA were significantly higher in IDA patients before treatment with iron supplements and decreases after treatment.14 They estimated that the reason could be due to the fact that in iron deficiency, the quaternary structure of the hemoglobin molecule was altered, and that glycation of the globin chain occurred more readily in the relative absence of iron.14

Van Heyningen et al reported that there was no difference in HbA1c concentration and IDA before and after treatment in non-diabetic patients. They reported that the difference is due laboratory testing.15 This was corroborated by a study by Hansen et al, who demonstrated that there was no difference in the HbA1c concentrations between IDA and healthy individuals.16

Corroborating our study, studies by Cogan et al, and el Agouza et al showed that the HbA1c levels were higher in patients with IDA and decreased significantly on treatment with iron supplements. According to them, elevated HbA1c levels in iron deficiency anemia could be explained by the assumption that if serum glucose remains constant, a decrease in the hemoglobin concentration might lead to an increase in the glycated fraction.17,18

In contrast, in a study by Sinha et al, there was a significant rise in the HbA1c levels 2 months after treatment with iron supplements in IDA patients. There have been a few studies on diabetic patients which has proven that controlled plasma glucose levels for 3 months correlates very well with controlled HbA1c. Hence, patients with controlled plasma glucose levels are expected to have A1C below 6.5%19.

Ferritin, the storage form of iron reflects its true status of iron in the plasma.20 We have assessed the levels of ferritin during the treatment of severely anemia patients. We observed that there was a considerable increase of ferritin levels on treatment in 1 and 2 months which was associated with marked rise in the hemoglobin levels. This results were corroborated by Nitin Sinha et al while in yet another study by Christy et al, no significance was found.

Raj et al investigated 86 patients with type 2 diabetes mellitus and demonstrated that serum ferritin positively correlated with HbA1c and was increased with increasing duration of disease, indicating that poor glycaemic control can contribute to elevated ferritin levels independent of iron status.

Conclusion

There is a significant association of HbA1c levels and Iron Deficiency Anemia according to our study. But there are few studies done in this area. This only reiterates the need of further investigations to be performed with more number of participants in order to estimate the significance of this association so as to address the situation in clinical practice.

Conflict of Interest: None

Source of Support: None

References:


