ORIGINAL RESEARCH ARTICLE

Effect of Iron Deficiency Anaemia on Hemoglobin A1c (HbA1c) Levels in Diabetic Patients in Tertiary Care Hospital

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Abstract:

Background: Diabetes mellitus has become a major health problem worldwide. American diabetes association has considered HbA1c levels < 6.5 % as a target for glycemic control and as a diagnostic criterion for diabetes. Anemia is common in diabetes mellitus. Previous studies on alteration of HbA1c in iron deficiency anemia (IDA) have conflicting results.

Objective: The primary aim of this study was to identify and compare effect of IDA on HbA1c levels among controlled diabetics (fasting glucose less than 126 mg/dl since last six months) and its variation according to the degree of anemia.

Methods: The present study is cross sectional study, including 70 controlled diabetics (35 iron deficiency anemia and 35 without anemia). HbA1c, complete haemogram, iron profile and fasting blood glucose were tested. Medical history was recorded.

Results: The mean HbA1c levels in controlled diabetics with and without IDA were 7.94 ± 1.45 and 6.22 ± 0.33 respectively ($p < 0.05$). The mean HbA1c levels in mild and moderate anemia was significantly raised as compared to controls whereas this rise was not found significant. In severe anemia the mean HbA1c was 8.86 ± 1.96 which was slightly low as compared to moderate grade anemia 8.93 ± 2.84.

Conclusion: In IDA falsely elevated HbA1c is independent of the blood glucose concentration in controlled diabetics. Hence, prior to alteration of treatment regimen based on HbA1c for diabetes,

IDA should be diagnosed and corrected. Concurrent evaluation for anemia is critical to correctly interpret glycemic status in Indian population with prevalent diabetes.

Keywords: HbA1c, Diabetes, Iron deficiency anemia

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Introduction:

WHO defines diabetes mellitus as a state of chronic hyperglycemia. Type 2 diabetes manifests in the late adult life and accounts for 95% of all cases(1). India leads the world with the largest number of diabetic subjects, thus being termed as the 'Diabetic Capital of World' (2).

Hemoglobin A1c (HbA1c), a glycated hemoglobin commonly used as a screening test for diabetes in clinical practice (3,4). When plasma glucose is consistently elevated, the non-enzymatic glycation of hemoglobin increases. This alteration reflects the glycemic status over the past 3 months (5). American Diabetes Association has recently endorsed HbA1c more than 6.5% as a diagnostic criterion for diabetes mellitus (6,7).

Besides blood sugar other conditions like hemolytic anemia, acute/chronic blood loss, pregnancy, hemoglobinopathies, uremia has also shown to affect HbA1c (8,9). Also, hemoglobin levels can be changed by different type of anemias (10). Iron deficiency anemia (IDA) can increase the red cell turnover which leads to increase in glycation of hemoglobin leading to higher HbA1c values (11).

There are studies to support the idea that diabetes is influenced by change in iron levels in the body (12,13).Studies have concluded that iron deficiency elevated HbA1c levels in

diabetic patients when compared with iron sufficient controls matched for fasting glucose (5, 15 ,16, 17, 18). Thus, iron status must be considered before making any therapeutic decisions based solely on HbA1c levels. The iron replacement therapy is thus important in diabetic patients as it would increase the reliability of HbA1c determination (5, 16). This study aimed at finding the effect on HbA1c in type 2 diabetes patients with diagnosed IDA in patients visiting the tertiary care hospital so that appropriate measures to control HbA1c levels can be taken before altering the treatment regimen for diabetes.

Material and Methods:

The present study was a cross sectional study conducted in BKL Walawalkar Rural Medical College, Sawarde. The study consists of 140 type 2 diabetic patients having >18yrs of age visiting to BKL Walawalkar Hospital from 15th April 2018 to 15th June 2018. Individuals with type 2 diabetes mellitus, more than 18 years of age and with fasting glucose less than 126 mg/dl since last six months were included in the study.

After exclusion of individuals with fasting glucose >126mg/dl, renal insufficiency (elevated serum urea, creatinine) hemoglobinopathies, pregnancy, hemolytic anemias; 70 patients with controlled plasma glucose levels were finalized for the study. They were divided into 2 groups-Group A: Study group including 35 diabetics >18yrs of age, diagnosed with iron deficiency anemia without hematinic treatment for anemia having Hemoglobin levels ≤12 gms% in males and ≤11 gms% in females were included in the study. They have been included in the study based on microcytic hypochromic blood picture, reduced red cell indices, low body iron stores and absence of stainable iron in bone marrow and Group B: 35 non-anemic diabetic controls with normal hemoglobin levels.

The Subjects with fasting plasma glucose more than 126 mg/dl or random glucose more than 200 mg/dl, pregnancy, renal failure, Hemolytic anemia, hemoglobinopathies, acute/ chronic blood loss, confirmed cases of malignancy were excluded from the study.

Demographic details including name, age, sex, residence, occupation, diet, Personal history – such as onset and duration of diabetes, Family history for diabetes, tobacco consumption in any form or alcohol consumption were taken. The written informed consent was also taken.

The plasma glucose was estimated by glucose oxidase- peroxidase method using EM 200. HbA1c was estimated by EM 200. Hemoglobin, MCV, MCH, MCHC were estimated by HORIBA YUMIZEN 500. On the basis of hemoglobin patients were categorized as having following grades of anemia - Mild: more than 9 gms%, Moderate: 7 to 9 gms% and Severe: less than 7 gms% The Peripheral blood smear examination was done to confirm microcytic hypochromic blood picture.

All data was tabulated using Microsoft Excel and statistical analysis was made using SPSS 16.0. Data was presented as mean +- SD for continuous variables and compared by student t-test. The Pearson's correlation coefficient (r) was used to determine correlation between two variables. P value <0.05 was considered significant.

Result and analysis:

Total 70 diabetic patients with controlled plasma glucose levels were chosen from total 140 patients. 35 diabetics were found to have iron deficiency anemia. Out of these 18 were females and 17 were males. Equal number of non anemic diabetic controls were also included.

The mean HbA1c levels in patients and controls were found to be 7.94 ± 1.45 and 6.22 ± 0.33 respectively. [Table 1]

Table No. 1: HbA1c levels in patients and controls

	Female 36		Male 34		Total 70	
Groups	Iron deficiency anemia (IDA)	non- anemics (NA)	Iron deficiency anemia (IDA)	non- anemics (NA)	Iron deficiency anemia (IDA)	non- anemics (NA)
Age (mean ± SD)	60 ± 14.18	54.83 ± 17.18	58.94± 16.22	63.29 ± 11.46	59.48 ± 14.99	58.94 ± 15.05
HbA1c (mean ± SD)	8.28 ± 1.33	6.35 ± 0.27	7.58 ±1.52	6.08 ± 0.33	7.94 ± 1.45	6.22 ± 0.33

Table No. 2: Comparison of mean HbA1c and red cell indices between anemic and non-anemic diabetics

Parameters	Iron deficiency anemia (IDA)	non- anemics (NA)	t Test	P Value
HbA1c	7.94 ± 1.45	6.22 ± 0.33	6.844	< 0.05
Hb	9.58 ± 1.72	13.03 ± 1.03	-10.150	< 0.05
MCV	70.17 ±5.21	83.26 ± 4.13	-11.643	< 0.05
MCH	23 ± 2.63	28.44 ± 2.21	-9.362	< 0.05
MCHC	30.77 ± 1.70	33.06 ± 0.98	-6.864	< 0.05

These results show that the mean HbA1c values in iron deficient diabetics were greater than the mean HbA1c in non-anemics and it was found to be statistically significant as ($p<0.05$) [Table No. 2].

The mean MCV, MCH, MCHC in controlled diabetics with anemia was found to be lower than the controls and was statistically significant ($p<0.05$).

The mean HbA1c in iron deficient diabetic male and female population was 7.58 ±1.52 and 8.28 ± 1.33 respectively whereas in non-anemics the values were 6.08 ± 0.33 and 6.35 ± 0.27 respectively [Table No. 1]. The rise in mean HbA1c was more in the females as compared to the males in both cases and controls [Figure No.1].

There was negative correlation between hemoglobin levels and HbA1c in anemic diabetics ($r= -0.478$) and it was found to be statistically significant. This observation implies that with the decrease of hemoglobin levels the HbA1c values were found to increase whereas, the correlation in non-anemic diabetics was not statistically significant. [Table No. 3].

According to degree of anemia when plotted, mild included 77% cases, moderate 8% and severe 14%. In all the degrees of anemia the mean HbA1c was found to rise significantly as compared to the iron sufficient controls. The mean HbA1c rise was higher in moderate and severe anemia as compared to mild anemia. This rise in severe anemia was found to be slightly lower (8.86 $\pm$ 1.96) than in moderate anemia(8.93 $\pm$ 2.84). [Table No. 4 & Figure No. 3]

Prevalence of iron deficiency anemia in adult type 2 diabetic patients visiting our tertiary care hospital was found to be 25%.

Figure No.1:

Gender wise distribution of mean HbA1c:

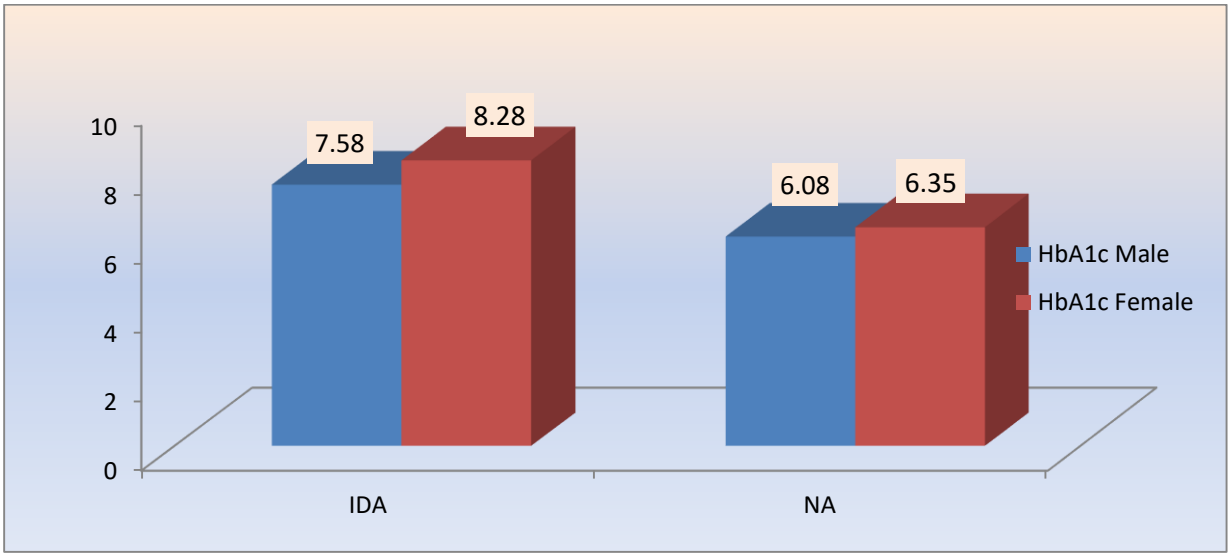


Table No. 3: Correlation between Hb and HbA1c

Groups	Number	Pearson's Correlation Coefficient (r)	P – value
IDA	35	- 0.478	< 0.05
NA	35	- 0.264	>0.05

Table No. 4: HbA1c variation according to degree of anemia

Study	Year	No. screened	Iron deficiency anemia (IDA)	non- anemics (NA)	Significance
Tarim et al [15]	1999	37	10.1 ±2.7	8.2 ±3.1	P < 0.05
Ng et al [9]	2010	15	7.4 ±0.2	6.9 ±0.1	P < 0.05
Christy et al [16]	2014	120	6.8 ±1.4	5.6 ±0.6	P < 0.05
Rajagopal et al[23]	2017	150	8.8 ±0.1	5.7 ±0.01	P < 0.05
Preset study	2018	70	7.94 ±1.45	6.22 ±0.33	P < 0.05

Table No. 5: comparison of present study with other studies

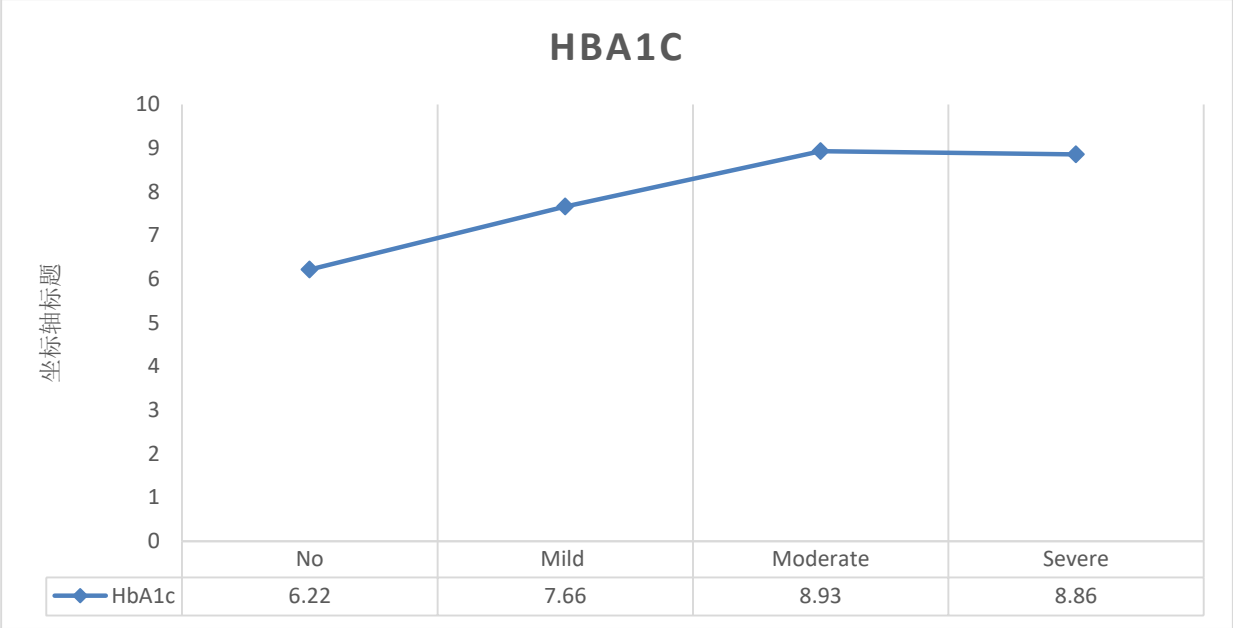
Groups	Number	Mean HbA1c
No anemia	35	6.22 ± 0.33
Mild anemia	27	7.66 ± 1.08
Moderate anemia	3	8.93 ± 2.84
Severe anemia	5	8.86 ± 1.96

No anemia to mild anemia t test: -7.44, p value <0.05

Mild to moderate anemia t test: -1.61, p value >0.05

Moderate to severe anemia t test: -1.61, p value >0.05

Figure No.2:



Discussion:

Glycated hemoglobin reflects the glycemic status when monitored, over the past 3months. Iron deficiency anemia is the most common form of anemia. According to many study anemia is found to be almost common in diabetics than non-diabetics [14, 24]. Increased HbA1c levels in IDA were explained by

1) Quaternary structure of Hemoglobin which is altered leading to rapid glycation of globin chain [23,25].
2) Increase in glycated fraction of hemoglobin due to decrease in total hemoglobin at a constant glucose level occurs because HbA1c is measured as a percentage of total hemoglobin [23].
3) Higher average age of circulating erythrocytes noticed in IDA due to reduced red cell production lead to increased HbA1c levels [23].

Only a few studies have investigated if IDA alters values of HbA1c till now, in-spite being widely used as a diagnostic tool for diabetes mellitus, thus leading to over or under diagnosis of diabetes mellitus when diagnosis is based on the cut off value <6.5% as approved by ADA [7].

The earliest study to investigate the effect of IDA on HbA1c levels was conducted by Brooks et al [19]. Results of which showed a spurious rise in glycated Hb in the presence of diabetes. The results of this study goes in accordance to the above finding, and also confirms study of Tarim et al [15]. The observation and results also coincide with study results of Christy et al [16], Ng et al [9] and Rajagopal et al [23] [Table 5]

Our results contradicted with Sharif et al [26], who reported no correlation between serum iron, ferritin and HbA1c levels in diabetic patients of either sex.

We also analyzed HbA1c results in different grades of anemia. Mean HbA1c was greater in all grades of anemia as compared to that of non-anemics. Mean HbA1c raised as severity worsened. This result was in accordance with results of Silva et al [21].

This study has got a significant relevance as IDA is highly prevalent in our country as, Malnutrition Related Diabetes Mellitus (MRDM) is increasing and most of the population belongs to the low and middle income groups.

This study had a small sample size and results were obtained from a single center and with a cross sectional study design, so we could not follow up after iron therapy. Hence, effect of IDA on HbA1c levels needs to be evaluated at mechanistic levels, so as to be assured about the outcome of the therapy and iron replacement therapy in diabetic patients with IDA needs to be considered.

Hence, prior to alteration of the treatment regimen based on HbA1c levels, for diabetes, IDA should be diagnosed and corrected. The present study suggests that concurrent measurement of Hb, HbA1c and iron status is critical to correctly interpret glycemic status in Indian population where IDA is highly prevalent.

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