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Impact of Iron Deficiency Anemia on Hba1c Levels among Non - Diabetic Patients

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Abstract
Introduction:
Glycated hemoglobin,HbA1c is the "gold standard" formonitoring glycemic control and is been used as a predictor of diabetic complications. Being one of the common forms of malnutrition, it attributes to 50% of all forms of anemia, globally. It's been found previously that reduced iron stores have a link with increased HbA1c, leading to false-high values of HbA1c in non-diabetic individuals. Even though iron deficiency anemia is the most common nutritional deficiency, the clinical evidence suggestive of the influence of Iron Deficiency Anemia on HbA1c is inconsistent.
Objectives: *To evaluate the association between Iron Deficiency Anemiaand HbA1c values.*
Methodology: *Observational Cross–sectional study was conducted on 50patients attending OPD / admitted to Government Rajaji Hospital & Madurai Medical College during the study period from February 2017 to July 2017. By Simple Random Sampling, patients with anemia, normal fasting and postprandial plasma glucose levels, normal liver function tests, normal blood urea and serum creatinine levels were recruited for this study.*
Results: *Twenty Five participants were in the iron deficiency anemia groupand 25 in the control (normal) group. The mean age of cases was 40.3 ± 10.7 years and mean age of controls was 38.4 ± 12.9 years. There were 27 (54 %) females and 23 (46 %) males. Mean Hb among cases was 8.48 ± 1.5 (5.4 to 10.9 gm/dL) and that among controls was 14.2 ±0.8 (12.3 -15.5 gm/dL). The total mean FBS and PPBS were 88.0 ± 7.8 and 124.0 ± 8.5 respectively. The mean HbA1c was 6.5 ± 0.6. The mean HbA1c for cases with Iron Deficiency Anemia was more than that for healthy controls (7.1 ± 0.3 and 6.0 ± 0.3 respectively) (p-value <0.0001).*
Conclusion: *Iron deficiency was associated with higher proportions ofHbA1c, which could cause problems in the diagnostic and therapeutic interpretation of the HbA1c concentrations. Hence, the iron status must be considered during the interpretation of the HbA1c.*
Key words: *iron deficiency, hemoglobin, glycated hemoglobin, diabetes.*

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I. Introduction

Glycated hemoglobin, HbA1c is the "gold standard" for monitoringglycemic control and is been used as a predictor of diabetic complications since 1980s.[1,2] HbA1c measurements correlate with mean serum glucose determinations over time; Glycated hemoglobin results from post-translational changes in the hemoglobin molecule, and their levels correlate well with glycemic levels over the previous six to 10 weeks.[3] Being a valid and reliable index of glycemic status, high concentrations of HbA1c is highly specific for diabetes. HbA1c has also been recommended as a diagnostic test for Diabetes Mellitus by the American Diabetes Association (ADA 2013).

Logistically, HbA1c requires a non – fasting random sample and is more advantageous compared to conventional oral glucose tolerance test, which requires a fasting sample[5].

Iron deficiency anemia is one of the major public health problems in India. Being one of the common forms of malnutrition, it attributes to 50% of all forms of anemia, globally. It's been found previously that reduced iron stores have a link with increased HbA1c, leading to false-high values of HbA1c in non-diabetic individuals.[5] Its alteration in other conditions such as hemolyticanemia, hemoglobinopathies, pregnancy, and vitamin B12 deficiency

Diagnostic Criteria for Diabetes: (ADA 2013)

Test	Threshold	Qualifier
Hemoglobin A1c	≥ 6.5%	Lab NGSP certified, standardized DCCT Assay
Fasting Glucose	≥ 126 mg/dL (7.0 mmol/L)	No caloric intake for at least 8 hours
2 – hour glucose	≥ 200 mg/dL (11.1 mmol/L)	After 75 g of anhydrous glucose
Random glucose	≥ 200 mg/dL (11.1 mmol/L)	Plus classic hyperglycemia symptoms or crisis
NGSP, National GlycohemoglobinStandardistation Program; DCCT, Diabetes control and complications Trial		

JUSTIFICATION OF THE STUDY

Even though iron deficiency anemia is the most common nutritional deficiency, the clinical evidence suggestive of the influence of Iron Deficiency Anemia on HbA1c is inconsistent. HbA1c is widely used as an important marker of glycemic control, and it is of utter importance to exclude factors which could spuriously elevate its levels. Hence, this study is been proposed in iron-deficient individuals with normal fasting blood sugar (FBS) and post prandial blood sugar (PPBS) levels to assess whether anemia has any effect on A1c levels, and anemia should be considered before making any therapeutic decisions based solely on HbA1c levels.

MATERIALS AND METHODS

This was an Observational Cross – sectional study conducted for a period of 6 Months (February 2017 to July 2017) at Department of General Medicine, Government Rajaji Hospital & Madurai Medical College, Madurai.

STUDY POPULATION

The study was conducted on 50 patients attending OPD / admitted to Government Rajaji Hospital & Madurai Medical College during the study period from February 2017 to July 2017.The sample size by Simple Random Sampling was 25 non diabetes patients with iron deficiency anemia and 25 controls at Government Rajaji hospital, Madurai

Inclusion Criteria

- Presence of anemia as defined by WHO Hb: <13.0 g/dl (adult males) <12.0 g/dl (non-pregnant women)
- Microcytic, hypochromic picture in peripheral blood smear
- Normal fasting and postprandial plasma glucose levels
- Normal liver function tests
- Normal blood urea, serum creatinine levels.

Exclusion Criteria

- Confirmed cases of diabetes mellitus (using two or more of the following: presence of symptoms related to diabetes, fasting blood glucose, 2 hours postprandial glucose, and oral glucose tolerance test).
- Hemoglobinopathies
- Hemolyticanemia
- Chronic alcohol ingestion
- Chronic renal failure
- Pregnant females
- Documented past history of gestational diabetes (GDM)
- History of Blood loss or blood transfusion in the past 3 months.
- Documented history of endocrinopathy with affect for glycemic control
- Current or prior use of medication with potential to increase or decrease HbA1c
- Haemoglobin concentration <6 g/dl or >16g/dl.

STUDY TOOL

A predesigned proforma was used to collect information of the study participants. The proforma had questions to collect information about the socio – demographic details of the participants, clinical history and signs suggestive of Anemia. Proforma also had details of estimated lab parameters like Complete Hemogram, Fasting and Post prandial blood Sugars and HbA1C.

STATISTICAL ANALYSIS

The collected data was entered in Microsoft Excel spreadsheet and analyzed using Statistical Package for Social Sciences (SPSS) version17.The analysis of data was carried out by entering the coded information and generating tables. The data was presented using descriptive statistics in form of tables and graphs. Results are expressed as proportions with 95% confidence interval. Univariate analysis was carried out using non – parametric Mann Whitney Test to compare the HBA1c values between two groups

ETHICAL CLEARANCE

Study proposal accepted by institute ethical committee,Madurai Medical College

II. Results And Interpretation

A total of 50 patients attending General Medicine OPD of Government Rajaji Hospital, Madurai were recruited for the study, of which 25 were in the iron deficiency anemia group and 25 in the control (normal) group. Of the 50 subjects, 23 (46 %) of them were in the age group of 20 – 39 years, whereas 23 (46 %) were in the 40 -59 years and remaining 4 (8 %) were more than 60 years

The age distribution among the cases with Iron Deficiency Anemia (IDA) and normal controls is shown in table. In the 20 – 39 years age group there were about 11 (44%) cases and 12 (48%) controls. In 40 -59 years category there were 13 (52%) cases and 10 (40%) controls whereas, in age group ≥ 60 years, there was one (4.0%) case and 3 (12%) controls. The mean age of cases was 40.3 ± 10.7 years and mean age of controls was 38.4 ± 12.9 years

Table : Comparison of Age in Case (IDA) and Healthy Control)

Age (in years)	Number of cases	Number of controls	Total
20-39	11 (44%)	12 (48%)	23
40-59	13 (52%)	10 (40%)	23
>=60	1 (4.0%)	3 (12%)	4
Total	25	25	50

Among the study participants, there were 27 (54 %) females and 23 (46 %) males .There were 15 (60 %) females and 10 (40 %) males in the cases and 12 (48 %) females and 13 (52 %) males in the controls.

Figure: Sex distribution of study participants

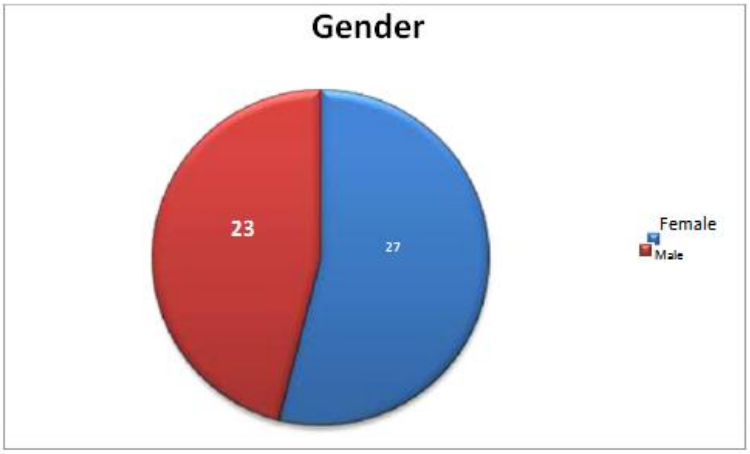


Table: Sex wise distribution of Cases (IDA) and Control (Healthy)

Gender	Number of cases	Number of controls	Total
Female	15	12	27
Male	10	13	23
Total	25	25	50

Presenting symptoms among patients with Iron Deficiency Anemia was enquired using proforma. Symptoms related to IDA like Fatiguability, Dyspnoea on Exertion, Fever, Giddiness, Gastro - intestinal Blood Loss and Palpitations were asked and depicted in Table. Fatiguability was found to be the most common symptom in 22 (88%) of cases, followed by Dyspnoea on Exertion in 11 (44%) cases.

Table: Presenting symptoms among cases

Symptoms among cases	Number	Percentage
Fatiguability	22	88
Dyspnoea on Exertion	11	44
Fever	3	12
Giddiness	4	16
GI Blood Loss	2	8
Palpitations	3	12

All the patients were subjected to clinical examination and signs related to IDA were assessed. The most common sign was found to be pallor (100%), followed by platynychia / Koilonychia in 9 (36 %) cases and Bald Tongue in 7 (28%) cases.

Table 5: Clinical signs among cases

Signs among cases	Number	Percentage
Pallor	25	100
Bald Tongue	7	28
Platynychia / Koilonychia	9	36
Pedal Oedema	3	12
Ejection Systolic Murmur	3	12
Venous Hum	2	8

The range of Hemoglobin among study participants is from 5.4 gm/dL to 15.5 gm/dL. Mean Hb among cases was 8.48 ± 1.5 (5.4 to 10.9 gm/dL) and that among controls was 14.2 ±0.8 (12.3 -15.5 gm/dL)

Mean Hb among males in case group was 9.3 ± 1.41 gm/dL and that of healthy controls was 15.7 ± 1.01 gm/dL. Likewise Mean Hb among females in case group was 7.9 ± 1.43 gm/dL and that of healthy controls was 12.6 ± 0.51 gm/dL

All participants with no history of Diabetes mellitus and normal Fasting and Post prandial blood sugars were recruited for this study. Parameters like Fasting (FBS), Post prandial blood Sugar (PPBS), and glycated Hemoglobin (HbA1c) were estimated for all the participants. The mean FBS and PPBS for all the participants were 88.0 ± 7.8 and 124.0 ± 8.5 respectively. The mean FBS among cases and controls were 88.4 ± 0.8 and 87.6 ± 7.8 respectively. There was no significant statistical difference among both the groups when compared using Mann Whitney test (p value = 0.72). The mean PPBS among cases were 124.8 ± 8.6 and controls were 123.2 ± 8.6, which was not statistically significant (p-value = 0.51).

Glycated Hemoglobin (HbA1c) was estimated for all participants and the mean HbA1c was 6.5 ± 0.6. The mean HbA1c for cases with Iron Deficiency Anemia was more than that for healthy controls (7.1 ± 0.3 and 6.0 ± 0.3 respectively) as depicted in Figure 9. There was a significant difference in mean HbA1c when comparing between cases and controls using Mann Whitney test. (p-value <0.0001).

Table Comparison of various parameters between cases and Controls:

Parameters	**IDA group (n=25)**	**Control group (n=25)**	**Total (n=50)**
Hb, g/dl	8.5 ± 1.6	14.2 ± 0.8	11.3 ± 3.1
Hct, %	30.7 ± 1.6	40.6 ± 4.4	35.6 ± 6.0
MCV, fl	74.4 ± 2.8	89.6 ± 2.9	82.0 ± 8.2
MCH, pg	22.6 ± 2.9	30.5 ± 2.3	26.6 ± 4.8
Ferritin, ng/ml	85.4 ± 8.5	193.7 ± 20.5	139.6 ± 56.9
HbA1c	7.1 ± 0.3	6.0 ± 0.3	6.5 ± 0.6
FBS	88.4 ± 0.8	87.6 ± 7.8	88.0 ± 7.8
PPBS	124.8 ± 8.6	123.2 ± 8.6	124.0 ± 8.5

Correlation between HbA1C and hematological parameters:

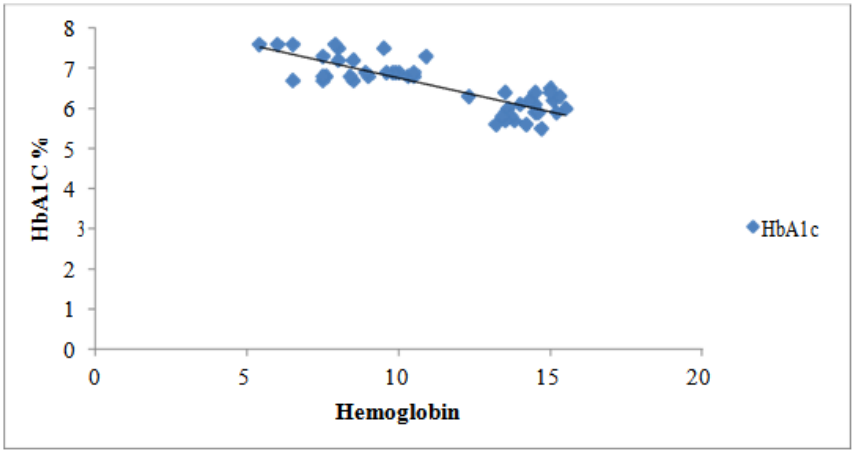
In our study, we did not find any significant correlation between hemoglobin and HbA1c (r = 0.388, *P* = 0.055). When we studied correlation for red cell indices like PCV, MCV, MCH, serum Ferritin, and HbA1c in IDA subjects, hematocrit (PCV) and MCH had a significant negative correlation against HbA1C (Pearson correlation coefficient r = -0.527; p-value =0.007 & r = -0.417; p-value =0.038 respectively). No significant correlation was found between HbA1c and MCV (r = -0.306, *P* = 0.137), and HbA1c and ferritin (r= -0.196, *P* = 0.348).

Table Correlation between HbA1C and hematological parameters:

HbA1c & hematological parameters	**Pearson correlation coefficient r**	**p-value**
Hemoglobin	-0.388	0.055
Hematocrit (PCV)	-0.527	**0.007**
MCH	-0.417	**0.038**
MCV	-0.306	0.137
S. Ferritin	-0.196	0.348

This is clearly evident from the following figure that there is a negative correlation between Hemoglobin and HbA1c. With decrease in Hemoglobin values, HbA1c increases. But this negative correlation is not statistically significant when analysed using pearson correlation coefficient (r value = - 0.388, *P* = 0.055

Figure 10: correlation between Hemoglobin and HbA1c:



III. Limitation

Our study did not involve any intervention. We did not estimate the values of HbA1c, Fasting Blood Glucose and post prandial blood glucose after iron therapy for few months. The effect of Iron deficiency anemia on HbA1c before and after iron supplementation would have been a better evidence to suggest that iron deficiency anemia increases the levels of HbA1c and to propose that iron deficiency has to be corrected before any diagnostic or therapeutic decision based on the HbA1c level.

IV. Conclusion:

HbA1c is not affected by the blood sugar levels alone. There are certain confounding factors when HbA1c is measured, especially thatof iron deficiency, which is the commonest of the nutritional deficiency diseases in India. Our study concludes that iron deficiency was associated with higher proportions of HbA1c, which could cause problems in the diagnostic and therapeutic interpretation of the HbA1c concentrations. Hence, the iron status must be considered during the interpretation of the HbA1c. concentrations in Diabetes mellitus. In diabetic patients with iron deficiency, iron replacement therapy would also increase the reliability of the HbA1c determinations.

CONFLICT OF INTEREST: NIL
FINANCIAL SUPPORT: SELF

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