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Original Research Article.

To Study the Correlation between Iron Deficiency Anemia and HbA1c Levels in Non Diabetics

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ABSTRACT

Purpose: Iron deficiency anemia is the most occurring form of anemia in India. Hemoglobin A1c (HbA1c) is used in diabetic patients as an maker to reflect glucose levels of the last 3 months. Like blood sugar levelsHbA1c levels are also affected by presence of variant hemoglobin, hemolytic anemia, nutritional anemias, uremia, pregnancy and acute blood loss. However, reports on the effects of iron deficiency anemia on HbA1clevels are inconsistent. We conducted this study with an aim to analyze the effects of iron deficiency anemia on HbA1clevels among non-diabetics.

Methods: 200 patients with Hb<10g/dl underwent peripheral blood film testing. All patients with microcytic hypochromic anemia underwent iron studies .Out of these, 100 non diabetic patients diagnosed with iron deficiency anemia underwent HbA1c test and data was statically analysed.

Results: We found that incidence of iron deficiency anemia was 54%. Serum iron and ferritin concentrations are inversely associated with HbA1c concentration and that HbA1c concentration tended to be higher in the presence of iron deficiency anemia.

Conclusion: This study found a positive correlation between iron deficiency anemia and increased HbA1c levels. Hence, Iron deficiency anemia has to be kept in mind before using the HbA1c to diagnose diabetes.

Keywords: Iron Deficiency Anemia, HbA1c, TIBC, Ferritin, Serum Iron.

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INTRODUCTION

Diabetes mellitus is a major health problem. Globally, an estimated 422 million adults are living with diabetes mellitus, according to the latest 2016 data from the World Health Organization (WHO) Type 2 diabetes makes up about 85-90% of all cases.[1]

The WHO (World Health Organisation) and the ADA (American Diabetes Association) have both advocated the use of HbA1c for diagnosing type 2 diabetes, (at a value of more than 6.5%) in addition to other criteria. The HbA1c test measures average glycaemia over 3 months, rather than instantaneous blood glucose levels. HbA1c has been used as an objective marker of average glycemic control for many years and has an accepted place in the monitoring of patients with diabetes. It is relied on for significant management decisions, such as initiation of insulin therapy.[2] HbA1c is formed in non-enzymatic glycation pathway by exposure of hemoglobin to plasma glucose. HbA1c is formed by the glycation of terminal valine at the β-chain of hemoglobin. Normal levels of plasma 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 over the previous three months. The test is limited to a three-month average though the lifespan of a red blood cell is four months (120 days), but all RBCs do not undergolysis at the same time, so HbA1c is taken as a limited measure of 3 months. American Diabetes Association has recently endorsed HbA1c ≥ 6.5% as a one of the diagnostic criterion for diabetes mellitus and 5.7 to 6.4 as prediabetes and below 5.7 as normal.[3]

Conditions that reduce red-blood cells lifespan, or decreases their mean age, falsely lower HbA1c test results[4] e.g. bleeding, haemoglobinopathies, haemolysis, renal anemia and vice versa. Conditions that increase the mean age of circulating erythrocytes may affect HbA1c in the opposite direction, in other words elevate HbA1c levels. Most studies investigating the effect of anemia on HbA1c are limited to the small sample groups, but data support that iron deficiency may lead to elevated HbA1c levels.[5]

The results of all studies done previously on this topic are conflicting and the exact mechanism as well as relationship between iron deficiency anemia on HbA1c levels is not yet known. Therefore, because of this lack of corresponding evidence and since no conclusive studies exist for this topic, we were prompted to conduct the current study to investigate the association of Iron Deficiency Anemia and HbA1c levels among non-diabetics.

MATERIALS AND METHODS

The present study is an observational study, which was conducted in the Department of Medicine, Sri Guru Ram Das Institute of Medical Sciences and Research, Vallah, Amritsar.

Inclusion Criteria

- Patients in the age group 18-60 years
- Males and adult non-pregnant females
- Without known diabetes
- Suffering from iron deficiency anemia

Exclusion Criteria

- Confirmed cases of type 2 diabetes mellitus
- Chronic renal failure
- Liver cirrhosis / hepatitis
- Blood loss or blood transfusion within 3 months of HbA1c assay
- Acute or recent haemorrhage including that caused by blood donation.
- Documented history of gestational diabetes (GDM)
- Current or prior use of medication with potential to increase or decrease HbA1c (includes antidiabetics, corticosteroids, statins, and antipsychotics)
- Pregnancy or pregnancy-related condition within three months of HbA1c assay.
- Patients on treatment with iron supplementation.

Methodology

A total of 5 ml of blood sample was taken in both red and purple vacutainers and samples were processed for complete blood counts. 200 patients with Hb<10g/dl underwent peripheral blood film testing. All patients with microcytic hypochromic anemia (n=120) underwent iron studies (serum iron, TIBC and serum ferritin) and out of these patients, 108 patients were diagnosed with iron deficiency anemia. Out of these patients, 100 were included in present study and underwent HbA1c test evaluation.

Laboratory Investigations

1. CBC by Automated Cell Counter.
2. Peripheral Blood Film.
3. Fasting blood Glucose by blood glucose meter.
4. Renal Function Test.
   a) Blood Urea Nitrogen by Urease/Glutamate dehydrogenase coupled enzymatic technique.
   b) Serum Creatinine by Kinetic Jaffe's method.
5. Iron Studies.
   a) Serum Iron Ferrizyme method on Imola fully automatic analyser.
   b) Serum ferritin Immuno turbid metric method.
   c) TIBC by Colorimetric method on Imola fully automatic analyser.
6. HbA1c Chromatographic method:

The chromatographic assay uses an HPLC instrument and ion exchange or affinity column to separate HbA1c molecules from other haemoglobin molecules. The HbA1c content is calculated based on the ratio of HbA1c peak area to the total haemoglobin peak.

Interpretation of HBA1c

4 - 5.6: Non Diabetic
5.7 - 6.4: Pre Diabetic Stage
>6.5: Diabetic
6.5 – 7.0: Well Controlled Diabetes
7.1 -8.0: Unsatisfactory Control
>8.0: Poor Control

RESULTS

Table 1 showed the distribution of type of anemia among 200 anaemic patients. 120 patients (60.0%) were diagnosed with microcytic hypochromic anemia, 35 (17.5%) were diagnosed with normocytic normochromic anemia and megaloblastic anemia was found among 45 (22.5%) patients.Among 120 with microcytic hypochromia108 (90%) were found iron deficient. Out of total 200 patients, 108 patients were diagnosed with iron deficiency anemia i.e. Incidence is 54%.

Table 2 depicted that the mean haemoglobin (±SD) of study population was 7.76 (±1.74). 82% had haemoglobin level ranges 6-10 and rest 18% had level less than 6. Mean serum iron deposit (±SD) of study population was 22.55 (±6.64). 84% had serum iron level less than 30 and rest 16% levels between ranges of 30-37. Mean serum Ferritin (±SD) of study population was 4.72 (±1.56). 68% had serum Ferritin levels between 0-3 followed by 18% with levels between 3-6 and 14% less than 6. Mean TIBC level (±SD) of study population was 422.38 (±92.73). 64% had TIBC levels above 402 and rest 36% had levels between ranges 251-402. Mean glycosylated hemoglobin level (±SD) of study population was 5.89 (±0.73). 46% had glycosylated hemoglobin levels ranges 5.7-6.4 followed by 31% with levels 4-5.6 and rest 23% had levels more than 6.5.

Table 1: Distribution of type of anemia and incidence of iron deficiency anemia

PBF	MCV	Number of patients N (%)	
Microcytic Hypochromic Anemia	≤ 82	120 (60)	Iron Deficiency 108 (90) Non-Iron Deficiency 12 (10)
Normocytic Normochromic Anemia	82-102		35 (17.5)
MegaloblasticAnemia	>102		45 (22.5)
Total			200 (100)

Table 2: Distribution of levels of biochemical parameters

Parameters	Number of patients(n)	Percent
Haemoglobin (Hb)		
Less than 6	18	18.0
6-10	82	82.0
Mean ± SD	7.76±1.74	
Serum Iron		
Less than 30	84	84.0
30-37	16	16.0
Mean ± SD	22.55±6.64	
Serum Ferritin		
0-3	68	69.0
3-6	18	18.0
>6	14	13.0
Mean ± SD	4.72±1.56	
TIBC		
251-402	36	30.0
>402	64	44.0
Mean ± SD	422.38±92.73	
HbA1c		
4-5.6	31	31.0
5.7-6.4	46	46.0
>6.5	23	23.0
Mean ± SD	5.89±0.73	
Total	100	100.0

Table 3: Association between Mean Serum Iron levels & HbA1c

Variables	Mean Serum Iron			
HbA1c	**N**	**Mean**	**Std. Deviation**	**p-value**
4-5.6	46	24.25	6.85	0.039
5.7-6.4	31	22.15	6.39	(Sig.)
>6.5	23	21.96	6.75	

TEST APPLIED: One-way ANOVA

Table 4: Association between Mean Serum Ferritin levels & HbA1c

Variables	Mean Serum Ferritin			
HbA1c	**N**	**Mean**	**Std. Deviation**	**p-value**
4-5.6	36	6.24	1.81	0.048
5.7-6.4	41	4.58	1.32	(Sig.)
>6.5	23	3.66	1.72	

TEST APPLIED: One-way ANOVA

Table 5: Association between Mean TIBC levels & HbA1c

Variables	Mean TIBC			
HbA1c	**N**	**Mean**	**Std. Deviation**	**p-value**
4-5.6	31	409.13	84.69	0.552
5.7-6.4	46	423.82	102.07	(NS)
>6.5	23	437.34	84.39	

TEST APPLIED: One-way ANOVA

Table 3 showed the association of different ranges of HbA1c with mean levels of serum iron store. After analysis using One-way ANOVA test an inverse association was observed and it was statistically significant p<0.05.

Table 4 showed the association of different ranges of HbA1c with mean levels of Ferritin store. After analysis using One-way ANOVA test an inverse association was observed and it was statistically significant p<0.05

Table 5 showed the association of different ranges of HbA1c with mean levels of TIBC. After analysis using One-way ANOVA it was statistically non-significant p>0.05.

DISCUSSION

Iron deficiency anemia is the most common form of anemia. In India, about 50% of anemia is attributed to iron deficiency. Children and women are the most vulnerable population. The factors contributing to iron deficiency anemia varies in different population.

HbA1c is glycated hemoglobin that can be used to assess the glycemic status of diabetic patient for the previous 3 months. Besides blood sugar, other conditions such as haemolytic anemias, hemoglobinopathies, iron deficiency anemia acute and chronic blood loss, pregnancy, and uremia have been shown to affect HbA1c levels.[6-15]So far HbA1c has been used as a valuable tool in monitoring the glycemic control in diabetics. HbA1c level of 6.5% has been proposed as a diagnostic cut off point.

In the present study out of total 200 anaemic patients (Hb<10g/dl), 120 (60%) patients were diagnosed to be suffering from with microcytic hypochromic anemia. All of these 120 patients underwent Serum iron, serum ferritin and TIBC testing. Iron deficiency was reported among 108 (90%) patients. So out of 200 anemic patients 108 patients were diagnosed with iron deficiency anemia i.e. 54% patients were found to have iron deficiency anemia. Similar results were observed by Mondalet al[16], they found that out of 150 patients diagnosed with microcytic hypochromic anemia 120 (80%) were iron deficient.

The Ministry of Health and Family Welfare, Government of India, in 2013, launched the National Iron plus Initiative as a comprehensive strategy to combat the public health challenge of IDA, as iron deficiency contributes to more than 50 % of anemia in our country.[17]

In the present study the mean Hb was 7.76 ±1.74. In males the mean Hb reported was 8.06±1.31, and in females 7.59±1.94 which corresponds to the moderate category of anemia.

In our study moderate anemia was observed in 62% and severe anemia in 18% of patients. In a study conducted by Gupta et al, out of 90% cases diagnosed with iron deficiency anemia they found that moderate anemia was observed in approx. 50% of the patients and severe category was observed only in 2% of the patients.[18] In the present study mean HbA1c was found to be 5.86±0.73 in patients with iron deficiency anemia. In patients with Hb1Ac range between 4-5.6 levels the mean serum iron was 24.25. For HbA1c range 5.7-6.4% the corresponding mean serum iron was 22.25. For HbA1c >6.5% the corresponding mean serum iron was 21.96. From the above observations, it is evident that the inverse association is present between HbA1c and mean levels of serum iron and this relation was statistically significant p<0.05 i.e. mean serum iron decreases as the level of HbA1c increases. In the present study similar association was observed between the level of serum ferritin and HbA1c. For Hb1Ac range 4-5.6%, the levels of the mean serum ferritin level were 6.24. For HbA1c range 5.7-6.4% the corresponding mean serum ferritin was 4.58. For HbA1c levels >6.5% the corresponding mean serum ferritin was 3.66. The association of HbA1c with mean levels of serum ferritin was found statistically significant i.e. p<0.05 i.e. mean serum ferritin decreases as the level of HbA1c increases.

We found this in agreement with the study conducted by Kalaskeret al[19], where they observed that the mean HbA1c of cases was 5.91 while it was 6.54 in healthy control. This difference of HbA1c between cases and controls for both the studied groups were found statistically significant. In another study conducted by Shanthiet al[20], the mean HbA1c of cases was 7.6 while it was 5.5 in healthy control. The difference of HbA1c between cases and controls for both the studied were found statistically significant. They postulated that serum iron and Ferritin concentrations are inversely associated with HbA1c concentration and that HbA1c concentration tended to be higher in the presence of iron deficiency anemia. In our study for Hb1Ac ranges 4-5.6%, the mean TIBC level was 409.12. For HbA1c levels 5.7-6.4% the corresponding mean TIBC was 423.82 and for HbA1c levels >6.5% the corresponding mean TIBC was 437.34. From the above values, although direct association was observed for HbA1c with mean levels of TIBC but it was found statistically non- significant p>0.05. Due to paucity of the literature in this study we could not compare the association of Hb1Ac with TIBC.

CONCLUSION

Iron deficiency anemia; the commonest nutritional deficiency worldwide but it was observed that the prevalence is higher in developing countries, and most vulnerable groups to IDA are women, children and adolescents. The present study concluded that the levels of HbA1c were increased significantly among patients with iron deficiency anemia. So, Iron deficiency anemia has to be kept in mind before using the HbA1c to diagnose diabetes. Large scale trials over longer durations may give accurate information about the influence of iron deficiency anemia over HbA1c levels. This will increase the reliability of HbA1c in diagnosing diabetes.

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