Section: Miscellaneous

Original Research Article

# EFFECT OF IRON DEFICIENCY ANEMIA ON HEMOGLOBIN A1C LEVELS IN DIABETIC PATIENTS: A STUDY AT TERTIARY CARE CENTRE

*Received : 19/12/2024*
*Received in revised form : 11/02/2025*
*Accepted : 27/02/2025*

*Keywords:*
*Iron deficiency anemia, Diabetes, Hemoglobin A1c (HbA1c), Peripheral blood smear, Red blood cell indices.*

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DOI: 10.47009/jamp.2025.7.1.193

Source of Support: Nil,
Conflict of Interest: None declared

*Int J Acad Med Pharm*
2025; 7 (1); 988-992

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## Abstract

**Background:** Iron deficiency anemia (IDA) is a global public health problem, especially among individuals with chronic illnesses such as diabetes mellitus. Hemoglobin A1c (HbA1c) is a crucial indicator of long-term glycemic control in diabetic patients. Various factors can influence HbA1c levels, with iron deficiency anemia being one of them. However, limited research has explored the association between HbA1c and IDA in diabetic individuals. This study aims to observe the effect of iron deficiency anemia on HbA1c levels in diabetic patients, examining potential mechanisms, clinical implications, and identifying areas for future research. **Materials and Methods:** A total of 299 patients (158 females and 141 males) attending the outpatient departments (OPDs) of NIIMS were included in our study. HbA1c and blood glucose levels were measured on Erba Chem 220 autoanalyzer. Complete blood count and histograms were obtained from 5-part automated hematology analyzer. Peripheral blood smears were prepared and stained for the typing of anemias. The patients were then categorized based on the values obtained and observations made. Among the 299 patients, 170 were found to be diabetic. Of the 170 diabetic patients, 98 had iron deficiency anemia. Statistical analysis was performed and an independent t-test was computed. The result was reported as mean ± SD. A P-value of less than 0.05 was considered statistically significant. **Result:** The mean hemoglobin (Hb), hematocrit (HCT), mean cell volume (MCV), mean cell hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC) were all reduced in the IDA group as compared to the non-IDA diabetic patients. Additionally, the HbA1c (%) level was lower in the IDA group (8.942±1.87) compared to the non-IDA diabetic patients (9.739±2.43), with a statistically significant difference ($p < 0.05$). **Conclusion:** HbA1c levels were significantly lower in diabetic patients with IDA compared to those without IDA. As a result, the authors caution against relying exclusively on HbA1c levels to monitor these patients, as this could lead to inaccuracies. Additionally, future research should involve a larger participant pool and utilize more advanced laboratory methods for a more comprehensive analysis.

## INTRODUCTION

The incidence of diabetes mellitus has been steadily increasing worldwide, with a particularly dramatic rise in developing nations.[1,2] The IDF Diabetes Atlas 10th edition reports that about 537 million adults (20-79 years) are living with diabetes. This number is predicted to rise to 643 million by 2030 and 783 million by 2045.[3] In diabetic patients, HbA1c is the gold standard for monitoring glycemic status over the past three months, aligning with the lifespan of red blood cells.[4,5] It offers a more reliable indicator of long-term glycemic control compared to routine blood glucose levels.[6]

HbA1c accounts for about 5% of total hemoglobin in non-diabetic individuals and is produced through the irreversible, non-enzymatic attachment of glucose to the N-terminal valine and internal lysine amino groups of the beta chain of adult hemoglobin.[5-8] The rate and extent of this glycation process depend on the blood glucose concentration that erythrocytes are exposed to over their 120-day lifespan.[6] Therefore, HbA1c reflects the average blood glucose concentration over the previous two to three months. However, interpreting HbA1c levels is complex because various conditions can affect the lifespan of red blood cells. These conditions include hemolytic anemias, hemoglobinopathies, acute or chronic blood loss, vitamin B12 and folate deficiency anemia, iron deficiency anemia, and uremia.[6,9-12]

Anemia is a major public health problem the world over. Globally, 1.62 billion people (24.8%) suffer from anemia,[1,13,14] with iron deficiency being the major cause, especially in developing countries. Therefore, it is crucial to assess the association between iron deficiency anemia and HbA1c, particularly in developing countries like ours where both iron deficiency anemia and diabetes mellitus are highly prevalent.

Various authors,[11,15,16] have observed that lower iron levels are associated with increased glycation of hemoglobin, leading to higher HbA1c values in diabetic and non-diabetic patients. However, some studies have reported no correlation between HbA1c levels and iron deficiency anemia (IDA) in patients and controls,[17-19] and a few studies have even observed a decrease in HbA1c levels in diabetic cases having iron deficiency anemia.[12,20-22] Therefore, the effect of iron deficiency on HbA1c levels remains conflicting.[11,12]

Given the inconsistent findings and limited research on the effects of IDA on HbA1c levels in diabetic patients, this study was conducted to investigate whether such an association exists. If confirmed, understanding this relationship is crucial for effective diabetes management.

## MATERIALS AND METHODS

The study was carried out in the Central laboratory at NIIMS, Greater Noida, over one year, from January 2022 to December 2022. This study included 299 (158 females and 141 males) patients aged 18 years and above who attended the outpatient departments (OPDs) of NIIMS. Venous blood samples were collected for hematological tests and HbA1c estimation. Patients were categorized based on their blood sugar and hemoglobin levels. Among the 299 patients, 170 were found to be diabetic (HbA1c ≥6.5%) and 129 had HbA1c levels below 6.5%. Of the 170 diabetic patients, 98 were diagnosed as having iron deficiency anemia, while 72 were non-anemic. Patients with anemias other than IDA, pregnant females, and patients having abnormal kidney and liver function tests were excluded from the study.

HbA1c and blood sugar levels were estimated using the Erba Chem 220 auto-analyzer. Hemoglobin concentration, red cell indices, and histograms were obtained from the Mindray BC 5130 automated 5-part hematology analyzer with standard calibration. Peripheral blood smears were prepared, stained with Leishman stain, and morphological abnormalities were noted. Anemia typing was based on parameters generated from the hematology analyzer, the position and shape of histograms, and peripheral blood smear findings. Subjects with low hemoglobin levels (less than 12 g/dL in females and 13 g/dL in males), reduced RBC indices (MCV < 80 fl, MCH < 27 pg, and MCHC < 31%), increased RDW, histogram patterns consistent with IDA (left shift and broad-based curve), and microcytic hypochromic morphology on peripheral blood smear were considered to have iron deficiency anemia. Statistical analysis was performed using independent t-test. Data were reported as mean ± SD, with a p-value of less than 0.05 considered statistically significant.

## RESULTS

This study was conducted to examine the effect of Iron Deficiency Anemia (IDA) on HbA1c levels in diabetic patients. The study comprised 299 patients aged 18 years and above, with 158 females (52.8%) and 141 males (47.2%) [Table 1]. Maximum patients belonged to 41-70 years of age (74.2%) [Table 2].

Of the 299 patients who underwent blood sugar and HbA1c analysis, 170 were diagnosed with diabetes, characterized by high blood sugar levels (fasting > 110 mg/dL and random > 140 mg/dL) and elevated HbA1c levels (HbA1c ≥ 6.5%) [Table 3].

On analysis of peripheral blood smears and autoanalyzer-derived RBC indices and histogram patterns of 170 diabetic patients, 98 cases (57.6%) of iron deficiency anemia were diagnosed. These patients had low Hb levels and reduced RBC indices with increased RDW. Histogram patterns and peripheral blood smear findings were also consistent with iron deficiency anemia [Table 4].

All hematological parameters and HbA1c levels were examined for both groups. Mean ± SD was calculated, and an independent t-test was used to compare the means of Hb, MCV, MCH, MCHC, and HbA1c between the IDA and non-IDA groups.

The results showed that the mean levels of hemoglobin (Hgb), mean cell volume (MCV), mean cell hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC) and HbA1c were lower in the IDA group as compared to the non-IDA diabetic individuals. Specifically, HbA1c (%) levels were significantly lower in the IDA group (8.942 ± 1.87) compared to the non-IDA diabetic group (9.739±2.43), with a statistically significant p-value [Table 5].

**Table 1: Sex distribution among the study population.**

| Gender | Number | Percentage (%) |
|---|---|---|
| Female | 158 | 52.8 |
| Male | 141 | 47.2 |
| Total | 299 | 100 |

**Table 2: Age-wise distribution of the study population**

| Age (years) | Number | Percentage (%) |
|---|---|---|
| 18-30 | 12 | 4.0 |
| 31-40 | 35 | 11.7 |
| 41-50 | 70 | 23.4 |
| 51-60 | 79 | 26.4 |
| 61-70 | 73 | 24.4 |
| > 70 | 30 | 10.0 |
| Total | 299 | 100 |

**Table 3: Distribution of study population based on HbA1c levels**

| Type of patient | Number/ Frequency | Percentage (%) |
|---|---|---|
| Diabetic | 170 | 56.9 |
| Nondiabetic | 129 | 43.1 |
| Total | 299 | 100 |

**Table 4: Distribution of diabetic patients based on presence of iron deficiency anemia**

| | Number | Percentage (%) |
|---|---|---|
| Anemic | 98 | 57.6 |
| Nonanemic | 72 | 42.4 |
| Total | 170 | 100 |

**Table 5: Independent t-test for hematological parameters in diabetic patients between the IDA and Non-IDA groups**

| Parameter | IDA | Non-IDA | t-test (95% confidence interval) | | |
|---|---|---|---|---|---|
| | | | P value | lower | Upper |
| Hb | 11.21±1.30 | 13.69±1.11 | <0.001 | -2.8633 | -2.1107 |
| HbA1c | 8.942±1.87 | 9.739±2.43 | 0.017 | -1.4497 | -0.1444 |
| MCV | 82.63±8.0 | 83.87±10.22 | 0.371 | -4.0279 | 1.5103 |
| MCH | 28.138±3.8275 | 29.123±2.3548 | 0.036 | 0.0644 | 1.9052 |
| MCHC | 33.974±2.1762 | 33.874±1.6263 | 0.720 | -0.6496 | 0.4497 |

## DISCUSSION

Glycated hemoglobin has been defined as the fast fraction hemoglobin (HbA1a, A1c) which elutes first during column chromatography with cation exchange resin.[6] HbA1C is a stable marker and less susceptible to temporary changes such as diet, exercise, or medications. Consequently, both the WHO (World Health Organization) and ADA (American Diabetes Association) have approved the use of HbA1C for the diagnosis or screening of type 2 diabetes.[5,23,24] The ADA has also endorsed HbA1C ≥6.5% as a diagnostic criterion for diabetes mellitus.[11,25]

Hemoglobin is exposed to the same glucose concentration as plasma because erythrocytes are readily permeable to glucose molecules.[1,12] Consequently, the amount of HbA1c is directly related to the average blood glucose level over the typical lifespan of a red blood cell.[26] The conversion of Hb A to HbA1c occurs throughout the lifespan of an erythrocyte. While HbA1c typically makes up about 5% of total hemoglobin in normal individuals, it can constitute up to 15% in diabetic patients.[1]

Iron deficiency anemia is the most common nutritional deficiency disease worldwide.[6,12,27] Studies indicate that glucose levels are influenced by the body's iron levels.[5,28] Iron modulates both the action and secretion of insulin.[5,29] Numerous studies have analysed the impact of iron deficiency anemia on HbA1c levels in individuals with and without diabetes, but the findings have been contradictory.

Various researchers have supported the theory that lower iron levels are associated with increased glycation of hemoglobin, which can result in elevated HbA1c values in both diabetic and non-diabetic patients.[11,15,16] It has been observed that changes in the quaternary structure of the hemoglobin molecule due to low iron levels lead to excessive glycation of the beta-globin chain.[5,12] In individuals diagnosed with diabetes, the higher glucose concentration accelerates this reaction, resulting in elevated HbA1c levels.[5,12]

Other conditions such as acute or chronic blood loss, hemolytic anemias, hemoglobinopathies, vitamin B12 and folate deficiency anemia, and uremia may also affect HbA1c levels.[6,9,10,11,12] In a study by Coban et al,[16] and El Agouza et al,[30] it was observed that lower hemoglobin levels at a constant glucose level can increase the glycated fraction of hemoglobin because HbA1c is measured as a percentage of total HbA. Additionally, research by Coban et al,[16] El-Agouza et al,[30] and Mudenda et al,[31] demonstrated that patients with iron deficiency anemia had higher HbA1c levels, which notably decreased following iron treatment.

Conversely, some studies have reported no significant difference in HbA1c levels between patients with iron deficiency anemia (IDA) and controls.[17-19] Some studies have even reported a decrease in HbA1c levels in iron deficiency anemia.[1,12,20-22] It is possible that participants in these studies had a higher degree of anemia than average, which could explain why their HbA1c levels were significantly lower than expected. Also, conditions that lead to early red blood cell clearance or increased production of reticulocytes in the body can result in falsely low HbA1c levels.[32]

In our study, we also observed significantly lower HbA1c levels in diabetic patients with iron deficiency anemia as compared to controls. The mechanism by which iron deficiency anemia (IDA) affects HbA1c levels has not been fully elucidated. Hence, the clinical impact of iron deficiency on HbA1c levels appears inconsistent.[11,12] Therefore, conducting more comprehensive studies with larger sample sizes among individuals with IDA would be beneficial to thoroughly investigate its impact on HbA1c levels.

## CONCLUSION

HbA1c levels in diabetic patients with iron deficiency anemia (IDA) are notably lower compared to diabetic patients without IDA. This suggests that relying solely on HbA1c screening in these patients may be misleading, prompting clinicians to carefully consider this factor before making treatment decisions. Addressing iron-deficiency anemia before using HbA1c for diabetes diagnosis or management is also advisable.

Future large-scale studies are essential to thoroughly investigate the impact of iron deficiency anemia on reducing HbA1c levels and to explore the mechanisms that contribute to reduced hemoglobin glycation in conditions like IDA, given the limited existing research in this area.

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