Original Research Paper

Volume - 15 | Issue - 06 | June - 2025 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Medicine

TO STUDY THE EFFECT OF IRON DEFICIENCY ANAEMIA ON GLYCOSYLATED HAEMOGLOBIN (HBA1C) IN NON-DIABETIC ADULTS

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ABSTRACT **Background:** Diabetes mellitus is a major health concern, with HbA1c serving as a key marker for diagnosis and management. However, iron deficiency anemia (IDA) may influence HbA1c levels, leading to potential misinterpretation of glycemic status. Given the high prevalence of IDA, understanding its impact on HbA1c is crucial for accurate diabetes diagnosis. Altered erythrocyte turnover in IDA may artificially elevate HbA1c levels, leading to potential misclassification. Therefore, assessing iron status alongside HbA1c is essential for precise evaluation of glycemic control. **Objective:** To analyze the effect of IDA on HbA1c levels in non-diabetic individuals and determine whether IDA alters its reliability as a diagnostic tool for diabetes. **Methods:** This case-control study was conducted at KD Medical College Hospital, Mathura, over 18 months, involving 120 participants (60 IDA cases, 60 controls). Patients were diagnosed with IDA based on hemoglobin levels, RBC indices, peripheral smear, and iron studies. Exclusion criteria included diabetes, chronic kidney disease, pregnancy, and obesity. Statistical analysis was performed using SPSS (version 25). **Results:** The mean age of the case group was 53.73 ± 19.97 years, and the control group was 50.16 ± 19.62 years ($p = 0.32$). Hemoglobin, MCV, MCH, and serum ferritin levels were significantly lower in IDA patients, while TIBC was higher ($p < 0.0001$). HbA1c levels were significantly elevated in the case group (8.42% ± 2.08) compared to controls (5.12% ± 0.53). Correlation analysis indicated a negative association between HbA1c and hemoglobin, MCV, MCH, serum ferritin, and serum iron, while TIBC showed a positive correlation. **Conclusion:** IDA is strongly associated with elevated HbA1c levels, potentially leading to an overestimation of glycemic control. These findings emphasize the need to assess iron status when interpreting HbA1c levels, particularly in populations at risk for iron deficiency.

KEYWORDS : Iron Deficiency Anemia, Glycosylated Hemoglobin, HbA1c, Non-Diabetic, Diabetes mellitus.

I. INTRODUCTION

Diabetes mellitus is one of the most prevalent and rapidly growing health conditions globally, posing a significant burden on public health systems. It is a leading cause of both morbidity and mortality, with its impact projected to rise sharply in the coming decades. In the year 2000, approximately 171 million individuals worldwide were affected by diabetes. Alarmingly, this number is expected to exceed 552 million by 2030, highlighting the urgent need for preventive measures and effective management strategies.[1] Early diagnosis of diabetes is critical, as timely and effective diabetes management can substantially reduce the risk of these complications and improve patient outcomes.[2]

Glycated hemoglobin (HbA1c) is a well-established biomarker for assessing glycemic control and plays a pivotal role in the management of diabetes mellitus (DM). HbA1c provides an average measure of blood glucose levels over a three-month period, reflecting long-term glycemic trends rather than short-term fluctuations. This makes it an invaluable tool not only for monitoring glycemic control in individuals with diabetes but also for predicting the risk of long-term complications associated with poor glucose regulation.[3] Both the American Diabetes Association (ADA) and the World Health Organization (WHO) acknowledge HbA1c levels as a key diagnostic marker for diabetes, establishing a threshold of 6.5% or higher as indicative of the disease.

The World Health Organization (WHO) identifies iron deficiency as the most prevalent nutritional deficiency globally, highlighting iron deficiency anemia (IDA) as a major public health concern. In India, IDA is especially widespread, with its primary causes including inadequate dietary iron intake, chronic blood loss (e.g., due to menstrual bleeding or gastrointestinal conditions), and impaired intestinal iron absorption.

Globally, With over 2 billion individuals affected globally, iron deficiency anemia (IDA) stands as the most widespread cause of anemia, highlighting its substantial influence on health and overall productivity. Addressing IDA requires a multipronged approach, including dietary interventions, iron supplementation, and public health measures to tackle underlying causes such as malnutrition and parasitic infections.

The impact of IDA on HbA1c levels remains a topic of debate in the literature. Some studies propose that HbA1c levels may be elevated in individuals with IDA, potentially due to a prolonged red blood cell lifespan, resulting in increased glycation.Conversely, other studies have reported significantly lower HbA1c levels in IDA patients compared to control groups, possibly linked to variations in red blood cell turnover and altered hemoglobin glycation dynamics.

Several studies have examined the relationship between iron deficiency anemia (IDA) and glycated hemoglobin (HbA1c) levels, with varying and often conflicting results. While some studies reported no significant differences in HbA1c levels between anemic patients and healthy controls, others suggested distinct patterns. For instance, A study by El-Agouza L et al. found that HbA1c levels were elevated in patients with IDA but significantly declined after iron therapy, suggesting a reversible effect. In contrast, more recent research by Sinha et al. indicated that both HbA1c levels and absolute HbA1c values increased following IDA treatment, underscoring the intricate and dynamic nature of this relationship.

The inconsistency across these studies underscores the need for further investigation into this phenomenon. Motivated by this gap in the literature, we aimed to examine the effects of IDA Our study focused on evaluating HbA1c levels specifically in non-diabetic Indian adults. The main aim was to assess whether individuals with IDA, despite not having diabetes, exhibited elevated HbA1c levels.If this association is confirmed, it would underscore the importance of correcting IDA before relying on elevated HbA1c levels for diagnostic or clinical decision-making, as untreated IDA could potentially lead to misleading interpretations of glycemic status.

II. MATERIALS & METHODS

The research was carried out in the Department of General Medicine at KD Medical College Hospital and Research Centre, Mathura, Uttar Pradesh, used a case control design from December 2022 to June

2024, with 120 patients. Inclusion criteria was patients of IDA (Diagnosed by Hemoglobin (Hb) Levels less than 12.1 g/dL for women and below 13.8 g/dL for men.Red Blood Cell Parameters: Mean Corpuscular Volume (MCV) lower than 80 fL and Mean Corpuscular Hemoglobin (MCH) less than 27 pg.Peripheral Smear Findings: Presence of microcytic hypochromic anemia. Iron Studies: Serum ferritin levels <15 µg/L, total iron-binding capacity (TIBC) >400 µg/dL, and serum iron levels <30 µg/dL.) both males and females >18 year of age, while exclusion criteria included cases of Sudden or prolonged blood loss, Anemia resulting from factors other than iron deficiency, Chronic kidney disease, confirmed cases of diabetes mellitus, cases with Impaired fasting glucose levels or Impaired postprandial glucose levels, Pregnant females and patients with obesity .

III. RESULTS

Table 1: Age Distribution of Case and Control Groups

Age Distribution (in years)	Case Group		Control Group	
	No. of Patients	Percentage	No. of Patients	Percentage
≤20	3	5.00	3	5.00
21-35	11	18.33	15	25.00
36-50	12	20.00	13	21.67
51-65	14	23.33	14	23.33
66-80	14	23.33	12	20.00
>80	6	10.00	3	5.00
Total	60	100.00	60	100.00
Mean±SD	53.73±19.97		50.16±19.62	
P-Value	0.32			

The age distribution was comparable between the case and control groups, with no significant difference (p = 0.32). The mean age in the case group was 53.73 ± 19.97 years, while in the control group, it was 50.16 ± 19.62 years. The distribution of patients across different age categories was similar, with the majority falling within the 36–80 years range.

Gender Distribution of Case and Control Groups

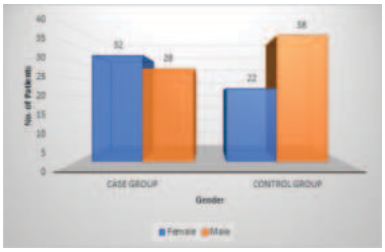

Figure 1 . Bar chart showing Gender Distribution of Case and Control Groups

Table 2: Comparison of Hemoglobin Levels Between Case and Control Groups

Parameter	Case Group		Control Group		P-Value
	Mean	SD	Mean	SD	
Haemoglobin	8.87	1.77	13.8	1.37	<0.0001

Table 3: Comparison of Serum Ferritin Levels Between Case and Control Groups

Parameter	Case Group		Control Group		P-Value
	Mean	SD	Mean	SD	
Serum Ferritin (ng/mL)	12.65	1.08	279.07	111.01	<0.0001

The comparison of serum ferritin levels between the case and control groups shows a significantly lower mean serum ferritin in the case group (12.65 ± 1.08 ng/mL) compared to the control group (279.07 ± 111.01 ng/mL), with a p-value of <0.0001. This substantial difference suggests a strong association between reduced serum ferritin levels and the condition being studied, indicating depleted iron stores, which is commonly seen in iron deficiency states.

Table 4: Comparison of Serum Iron Levels Between Case and Control Groups

Parameter	Case Group		Control Group		P-Value
	Mean	SD	Mean	SD	
Serum Iron (mcg / dL)	24.93	2.73	142.4	26.76	<0.0001

Table 5: Comparison of HbA1c Levels Between Case and Control Groups

Parameter	Case Group		Control Group		P-Value
	Mean	SD	Mean	SD	
HbA1c (%)	8.42	2.08	5.12	0.53	<0.0001

The analysis of HbA1c levels between the case and control groups revealed a significantly higher mean HbA1c in the case group (8.42% ± 2.08) compared to the control group (5.12% ± 0.53), with a p-value of <0.0001. This statistically significant difference suggests that individuals in the case group exhibit substantially elevated HbA1c levels, which may indicate impaired glycemic regulation or an underlying metabolic alteration in comparison to the control group.

Table 6: Comparison of HbA1c Levels Across Different Anaemia Severity Groups

Parameter	Case Group						P-Value
	Mild Anaemia (n=21)		Moderate Anaemia (n=30)		Severe Anaemia (n=9)		
	Mean	SD	Mean	SD	Mean	SD	
HbA1c (%)	7.85	1.8	8.49	2.02	9.53	2.36	0.11

The analysis of HbA1c levels across different anemia severity groups reveals a trend of increasing HbA1c with worsening anemia, though the difference is not statistically significant (p = 0.11). Patients with mild anemia had a mean HbA1c of 7.85% ± 1.8, while those with moderate anemia had a higher mean of 8.49% ± 2.02. The highest HbA1c levels were observed in the severe anemia group, with a mean of 9.53% ± 2.36. Although these findings suggest a potential association between anemia severity and elevated HbA1c levels, the lack of statistical significance indicates that additional studies with larger sample sizes may be required to confirm this relationship.

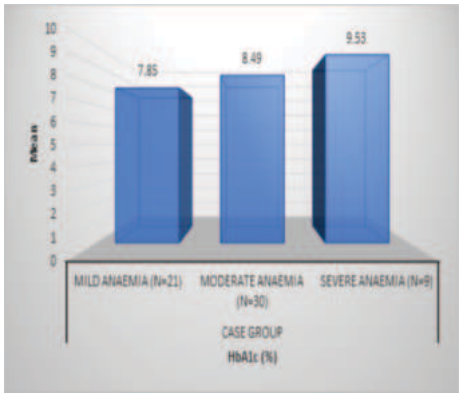

Figure 2 . Bar Chart Showing Comparison of HbA1c Levels Across Different Anaemia Severity Groups

Table 10: Pearson Correlation Between HbA1c and Various Hematological Parameters

Pearson Correlation	HbA1c (%)	
	r-value	p-value
Hb (gm/dl)	-0.29	0.02
MCV (fL)	-0.44	0.0004
MCH (pg)	-0.28	0.021
SERUM FERRITIN (ng/mL)	-0.39	0.002
TIBC (mcg/dL)	0.36	0.004
SERUM IRON (mcg / dL)	-0.25	0.04

The Pearson correlation analysis between HbA1c and various hematological parameters reveals significant associations. Hemoglobin (Hb) showed a weak negative correlation with HbA1c (r = -0.29, p = 0.02), indicating that lower hemoglobin levels might be associated with higher HbA1c values. Mean corpuscular volume (MCV) had a moderate negative correlation (r = -0.44, p = 0.0004), suggesting that smaller red blood cells may be linked to higher HbA1c levels. Mean corpuscular hemoglobin (MCH) also showed a weak negative correlation (r = -0.28, p = 0.021). Serum ferritin exhibited a moderate inverse correlation (r = -0.39, p = 0.002), while total iron-binding capacity (TIBC) was positively correlated (r = 0.36, p = 0.004), indicating that iron deficiency may influence HbA1c levels. Serum iron showed a weak negative correlation with HbA1c (r = -0.25, p = 0.04). These findings suggest that iron metabolism and erythrocyte indices may impact HbA1c values.

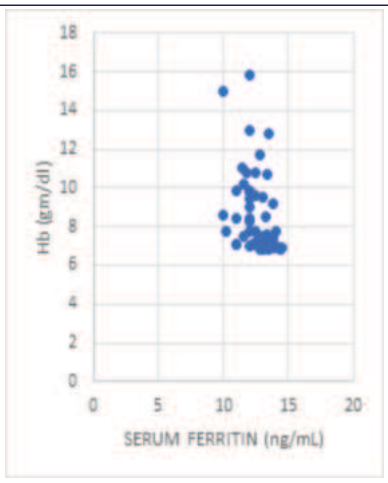

Figure 3. Scatter Plot Depicting Correlation Between HbA1c and Serum Ferritin.

IV. DISCUSSION

The age distribution was comparable Between the case and control groups, the difference was not statistically significant (p = 0.32).The mean age in the case group was 53.73 ± 19.97 years, whereas in the control group, it was 50.16 ± 19.62 years. Most participants in both groups fell within the 36–80 years range.

Bansal R K et al[1] observed that in an IDA cohort (n=100), the mean age was 43.39 ± 18.14 years, while in the control group (n=100), it was 42.51 ± 18.64 years, showing a close similarity between the two groups.

Gharde C et al[11] noted a varying age distribution among IDA patients: 8.9% (n=5) were younger than 25 years, 33.9% (n=19) fell between 25-35 years, 25% (n=14) were aged 36-45 years, 21.4% (n=12) belonged to the 46-55 years range, 7.2% (n=4) were 56-65 years, and only 3.6% (n=2) were older than 65 years.

Although the age range varies across studies, Krishna B M et al[12] reported a lower mean age of 35.6 ± 10.97 years, with participants between 20-50 years.

Hemoglobin Levels

The case group had significantly lower hemoglobin levels than the control group, with a mean of 8.87 ± 1.77 g/dL versus 13.8 ± 1.37 g/dL (p < 0.0001), indicating a high prevalence of anemia, likely due to iron deficiency or other hematological disorders.

Similarly, Coban E et al[13] found that the IDA group had a mean Hb level of 10.8 ± 1.2 g/dL before treatment, which significantly rose to 12.7 ± 0.96 g/dL post-treatment, while the control group had 13.6 ± 0.9 g/dL. In contrast, Gharde C et al[1] reported an even lower mean Hb level of 6.74 ± 3.72 g/dL in IDA patients.

Although Krishna B M et al[1] also observed significantly reduced hemoglobin levels in the IDA group (8.74 ± 1.98 g/dL) compared to controls (12.90 ± 0.54 g/dL, p < 0.01), a study from Delhi, India further reinforced that anemic patients had markedly lower Hb levels than healthy individuals (p < 0.01).[1]

Serum Ferritin Levels

The case group had significantly lower serum ferritin levels (12.65 ± 1.08 ng/mL) compared to the control group (279.07 ± 111.01 ng/mL, p < 0.0001), highlighting a strong link between low ferritin levels and iron deficiency.

Similarly, Janice D S et al[1] reported a mean ferritin level of 18.17 ± 16.14 pg/dL, with values ranging from 1.16 to 69.32 pg/dL. In contrast, Coban E et al[13] found that ferritin levels increased from 3.68 ± 1.78 ng/mL pre-treatment to 15.7 ± 1.88 ng/mL post-treatment but remained lower than the control group's 22.7 ± 6.3 ng/mL.

Although Bansal RK et al[1] observed markedly lower ferritin levels in IDA patients (9.86 ± 2.67 ng/mL) compared to controls (76.01 ± 9.03 ng/mL, p < 0.001), Gharde C et al[1] reported a relatively higher mean ferritin level of 56.28 ± 64.26 ng/mL in the IDA group.

HbA1c Levels Across Different Anaemia Severity

The findings indicate a trend of increasing HbA1c with worsening anemia, although the difference is not statistically significant (p = 0.11). The highest HbA1c levels were observed in the severe anemia group (9.53% ± 2.36), suggesting a possible association between anemia severity and elevated HbA1c. However, the lack of statistical significance underscores the need for larger studies to confirm this relationship.

Gharde C et al[11] analyzed anemia severity based on HbA1c levels. Among patients with moderate anemia (n=14), 71.5% had HbA1c between 5.6-6.5%, while 7.1% had levels between 6.6-7.5%. In severe anemia (n=42), 42.8% had HbA1c between 6.6-7.5%, showing a potential upward trend.

Pearson Correlation Between HbA1c And Various Hematological Parameters

The Pearson correlation analysis shows significant HbA1c levels were found to be significantly associated with various hematological markers. Hemoglobin (r = -0.29, p = 0.02), mean corpuscular volume (MCV) (r = -0.44, p = 0.0004), mean corpuscular hemoglobin (MCH) (r = -0.28, p = 0.021), serum ferritin (r = -0.39, p = 0.002), and serum iron (r = -0.25, p = 0.04) all showed inverse relationships with HbA1c. In contrast, total iron-binding capacity (TIBC) exhibited a positive correlation (r = 0.36, p = 0.004). These results suggest that iron-related parameters may have a significant impact on HbA1c levels.

Janice D S et al[1] reported positive correlations of HbA1c with ferritin (r = 0.351, p = 0.027), Significant positive correlations were observed between HbA1c levels and various hematological parameters, including hemoglobin (r = 0.839, p < 0.001), mean corpuscular volume (MCV) (r = 0.504, p < 0.001), mean corpuscular hemoglobin (MCH) (r = 0.606, p < 0.001), and mean corpuscular hemoglobin concentration (MCHC) (r = 0.523, p < 0.001). Additionally,

Bansal RK et al[1] found negative correlations of HbA1c with serum iron (r = -0.229, p = 0.02) and ferritin (r = -0.341, p = 0.001), while TIBC had a weak positive correlation (r = 0.183, p = 0.06, not significant).

Elsheikh E et al[1] observed weak, non-significant correlations for Hb (r = 0.086, p = 0.593) and hematocrit (r = 0.058, p = 0.718). MCV showed a significant negative correlation (r = -0.338, p = 0.031), while ferritin had a strong inverse correlation (r = -0.717, p < 0.001), linking higher ferritin levels to lower HbA1c.

V. CONCLUSION

Our findings indicated a strong correlation between iron deficiency and an increased prevalence of elevated HbA1c levels.This finding suggests that iron-deficient individuals may exhibit higher HbA1c levels independent of glycemic status, potentially leading to an overestimation of long-term blood glucose control. As a result, iron deficiency could interfere with the accurate diagnosis and management of uncontrolled diabetes mellitus, increasing the risk of misclassification and inappropriate treatment decisions. These findings highlight the importance of considering iron status when interpreting HbA1c levels, particularly in populations at risk for iron deficiency.

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