Section: General Medicine

Original Research Article

IMPACT OF MICROCYTIC ANEMIA ON HBA1C LEVELS IN NON-DIABETIC ADULTS: A CASE-CONTROL STUDY

Gudipati Prabhakar Siva[1], Rosaiah Duddu[2], Kanikalla Nagarjuna[3]

[1,2,3]Assistant Professor, Department of General Medicine, GMC, Guntur., India.

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Corresponding Author:
Dr. Gudipati Prabhakar Siva,
Email: prabhakarmedico@gmail.com

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ABSTRACT

Background: Glycated hemoglobin (HbA1c) is widely used for the diagnosis and monitoring of diabetes mellitus. However, several non-glycemic factors, including iron deficiency-related microcytic anemia, may influence HbA1c values and affect its diagnostic reliability. This study aimed to evaluate HbA1c levels in non-diabetic adults with microcytic anemia and assess their association with hematological parameters. **Materials and Methods:** This hospital-based case-control study was conducted in the Department of General Medicine, Government General Hospital, Guntur, from June 2023 to November 2024. Sixty non-diabetic adults were enrolled, comprising 30 patients with microcytic anemia (cases) and 30 age- and sex-matched healthy controls. Hemoglobin, mean corpuscular volume (MCV), fasting blood glucose (FBS), postprandial blood glucose (PPBS), and HbA1c levels were measured. Comparisons between groups were performed using the independent Student's t-test, and correlations were assessed using Pearson's correlation coefficient. **Results:** The mean hemoglobin and MCV values were significantly lower among cases than controls (9.93 ± 1.15 g/dL vs 14.36 ± 1.34 g/dL and 70.57 ± 6.32 fL vs 88.44 ± 4.01 fL, respectively; $p<0.001$). FBS and PPBS levels were comparable between the two groups ($p>0.05$). Despite similar glycemic profiles, mean HbA1c levels were significantly higher among cases than controls (6.80 ± 0.53% vs 5.41 ± 0.43%; $p<0.001$). Pearson correlation analysis demonstrated significant negative correlations between HbA1c and hemoglobin ($r = -0.761$, $p<0.001$) and between HbA1c and MCV ($r = -0.705$, $p<0.001$). A strong positive correlation was observed between hemoglobin and MCV ($r = 0.889$, $p<0.001$). **Conclusion:** Microcytic anemia is associated with significantly elevated HbA1c levels in non-diabetic adults despite normal blood glucose levels. HbA1c showed significant inverse correlations with hemoglobin and MCV, indicating that increasing severity of anemia and microcytosis is associated with higher HbA1c values. These findings suggest that microcytic anemia may lead to spuriously elevated HbA1c levels and potential misclassification of glycemic status. Therefore, hematological parameters should be considered while interpreting HbA1c values in individuals with microcytic anemia.

INTRODUCTION

Glycated hemoglobin (HbA1c) is a widely accepted marker of long-term glycemic control and reflects the average blood glucose concentration over the preceding two to three months. Owing to its convenience, reproducibility, and strong association with diabetic complications, HbA1c has been recommended for both diagnosis and monitoring of diabetes mellitus by major professional organizations.[1,2] However, HbA1c values are influenced by several non-glycemic factors that can affect its reliability.[3]

Iron deficiency anemia (IDA), the commonest cause of microcytic anemia worldwide, has been recognized as an important factor that can falsely elevate HbA1c levels independent of blood glucose concentration. Proposed mechanisms include prolonged erythrocyte lifespan, increased oxidative stress, and alterations in hemoglobin structure that facilitate glycation.[4,5] Several studies have demonstrated significantly higher HbA1c levels in non-diabetic individuals with iron deficiency anemia compared to healthy controls.[6,7]

In the Indian context, where both iron deficiency anemia and diabetes are highly prevalent, hematological factors including IDA have been shown to contribute to spuriously elevated HbA1c values and apparent over-diagnosis of prediabetes.[8] Similar findings have been reported in other

populations, highlighting the risk of diagnostic misclassification when relying solely on HbA1c.[9]
Despite growing evidence regarding the influence of iron deficiency anemia on HbA1c levels, data from Indian adults with microcytic anemia remain relatively limited and inconsistent. Therefore, the present study was undertaken to evaluate HbA1c levels in non-diabetic adults with microcytic anemia and to assess the association between hematological parameters and HbA1c levels.

Objectives

Primary Objective

To compare HbA1c levels between non-diabetic adults with microcytic anemia and age- and sex-matched healthy controls.

Secondary Objective

To evaluate the correlation between hematological parameters (hemoglobin and mean corpuscular volume) and HbA1c levels in non-diabetic adults with microcytic anemia.

MATERIALS AND METHODS

Study Design: This was a hospital-based case-control study.

Study Period: The study was conducted from June 2023 to November 2024.

Study Setting: The study was conducted in the Department of General Medicine, Government General Hospital, Guntur, Andhra Pradesh, India.

Study Population: A total of 60 non-diabetic adults were included in the study, comprising 30 patients with microcytic anemia (cases) and 30 age- and sex-matched healthy controls.

Inclusion Criteria

Cases

- Adults aged ≥18 years
- Hemoglobin <13 g/dL in males and <12 g/dL in females
- Mean corpuscular volume (MCV) <80 fL
- Peripheral smear showing microcytosis

Controls

- Age- and sex-matched healthy individuals with normal hemoglobin and MCV values

Exclusion Criteria

- Acute or chronic blood loss
- Hemolytic anemia
- Hemoglobinopathies
- Chronic kidney disease
- Pregnancy
- Known diabetes mellitus
- Impaired fasting glucose
- Impaired glucose tolerance
- First-degree family history of diabetes mellitus
- Obesity

Laboratory Evaluation

Demographic details, clinical findings, and laboratory parameters were recorded using a structured proforma. Blood samples were collected for complete blood count, red cell indices, peripheral smear examination, fasting blood glucose, postprandial blood glucose, and HbA1c estimation.

Study Procedure

Eligible participants were enrolled after obtaining informed consent. Detailed clinical history and demographic data were recorded using a structured proforma. Venous blood samples were collected under aseptic precautions for complete blood count, red cell indices, peripheral smear examination, fasting blood glucose, postprandial blood glucose, and HbA1c estimation. Participants fulfilling the criteria for microcytic anemia were included as cases, while age- and sex-matched healthy individuals served as controls. Hematological parameters and HbA1c levels were compared between the two groups, and their correlations were analyzed.

Statistical Analysis

Data were analyzed using SPSS software version 28. Continuous variables were expressed as mean ± standard deviation. Comparison between groups was performed using the independent Student's t-test. Correlation between hematological parameters and HbA1c levels was assessed using Pearson's correlation coefficient. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 60 non-diabetic adults were included in the study, comprising 30 patients with microcytic anemia (cases) and 30 age- and sex-matched healthy controls. The baseline demographic characteristics of the study participants are presented in [Table 1]. Both groups had identical age and gender distributions owing to the matched study design. Half of the participants (50.0%) belonged to the 41–60 years' age group, while males constituted 53.3% of the study population.

Table 1: Baseline demographic characteristics of study participants

Variable	Cases (n=30)	Controls (n=30)
Age 20–40 years	7 (23.3%)	7 (23.3%)
Age 41–60 years	15 (50.0%)	15 (50.0%)
Age 61–80 years	8 (26.7%)	8 (26.7%)
Male	16 (53.3%)	16 (53.3%)
Female	14 (46.7%)	14 (46.7%)

Data expressed as n (%). Cases and controls were age- and sex-matched.

The comparison of hematological and glycemic parameters between cases and controls is shown in Table 2. Fasting and postprandial blood glucose levels were comparable between the two groups and did not differ significantly. However, mean hemoglobin and MCV values were significantly

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lower among cases compared to controls. Despite similar glycemic status, mean HbA1c levels were significantly higher among patients with microcytic anemia (6.80 ± 0.53%) compared with controls (5.41 ± 0.43%), with a mean difference of 1.39% ($p<0.001$).

Table 2: Comparison of hematological and glycemic parameters between cases and controls

Parameter	Cases (n=30) Mean ± SD	Controls (n=30) Mean ± SD	p-value
FBS (mg/dL)	89.73 ± 8.26	88.80 ± 7.31	>0.05
PPBS (mg/dL)	118.13 ± 10.57	116.53 ± 9.44	>0.05
Hemoglobin (g/dL)	9.93 ± 1.15	14.36 ± 1.34	<0.001
MCV (fL)	70.57 ± 6.32	88.44 ± 4.01	<0.001
HbA1c (%)	6.80 ± 0.53	5.41 ± 0.43	<0.001

Independent Student's t-test.

The significant difference in HbA1c levels between cases and controls is illustrated in [Figure 1].

Pearson correlation analysis demonstrated a strong positive correlation between MCV and hemoglobin ($r = 0.889$, $p<0.001$). Both MCV and hemoglobin showed significant negative correlations with HbA1c levels. The correlation coefficient between MCV and HbA1c was −0.705 ($p<0.001$), while that between hemoglobin and HbA1c was −0.761 ($p<0.001$), as shown in [Table 3].

Table 3: Correlation of hematological parameters with HbA1c

Variables	Pearson correlation coefficient (r)	p-value
MCV vs HbA1c	-0.705	<0.001
Hemoglobin vs HbA1c	-0.761	<0.001
MCV vs Hemoglobin	+0.889	<0.001

The inverse relationship between MCV and HbA1c is further illustrated in [Figure 2], where decreasing MCV values were associated with progressively higher HbA1c levels.

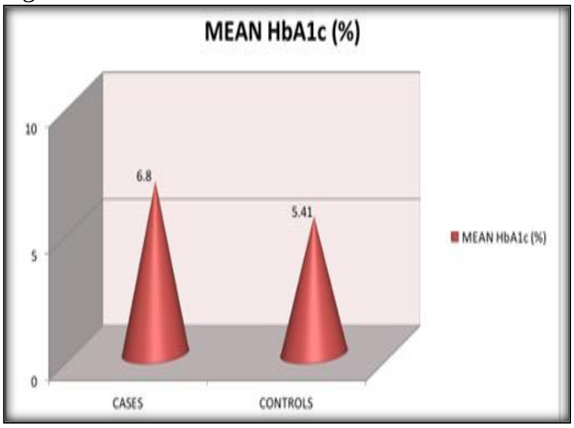

Figure 1: Comparison of mean HbA1c levels between cases and controls

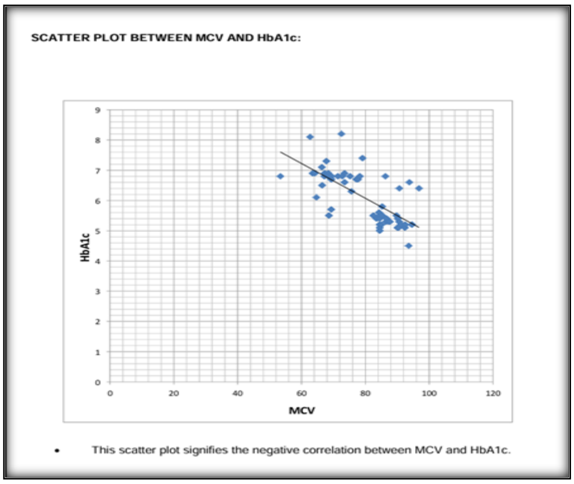

Figure 2: Scatter plot showing correlation between MCV and HbA1c levels

DISCUSSION

The present study demonstrated significantly higher HbA1c levels among non-diabetic adults with microcytic anemia compared to age- and sex-matched healthy controls despite comparable fasting and postprandial blood glucose levels. The mean HbA1c level in cases was 6.80 ± 0.53%, compared to 5.41 ± 0.43% in controls ($p<0.001$). These findings suggest that microcytic anemia may independently influence HbA1c values and lead to spuriously elevated results in the absence of true hyperglycemia. Similar observations were reported by Coban et al., who demonstrated significantly higher HbA1c levels in patients with iron deficiency anemia compared to healthy controls, and by Sinha et al., who observed elevated HbA1c values that decreased following correction of iron deficiency.[10,11]

The present study also demonstrated significant negative correlations between HbA1c and both hemoglobin ($r = -0.761$, $p<0.001$) and MCV ($r = -0.705$, $p<0.001$), indicating that worsening anemia and microcytosis are associated with progressively higher HbA1c levels. Similar inverse relationships have been reported by Tarim et al. and Rajagopal et al., who observed that lower hemoglobin levels and red cell indices were associated with higher HbA1c values in non-diabetic individuals with iron deficiency anemia.[12,13] The probable mechanisms include prolonged erythrocyte survival and increased glycation of hemoglobin in iron-deficient states, resulting in elevated HbA1c levels independent of blood glucose concentration.

The clinical implications of these findings are considerable, particularly in populations with a high prevalence of iron deficiency anemia. Elevated HbA1c values in individuals with microcytic anemia may result in misclassification of glycemic status and

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inappropriate diagnosis of prediabetes or diabetes. Guo et al. highlighted the importance of recognizing hematological factors that influence HbA1c interpretation and emphasized caution when using HbA1c as a sole diagnostic tool in patients with anemia.[14] Therefore, assessment of hemoglobin levels and red cell indices should be considered when interpreting HbA1c values, especially when HbA1c results appear discordant with plasma glucose measurements.

CONCLUSION

Microcytic anemia is associated with significantly elevated HbA1c levels in non-diabetic adults despite normal blood glucose concentrations. HbA1c showed significant negative correlations with both hemoglobin levels and mean corpuscular volume, indicating that increasing severity of anemia and microcytosis is associated with higher HbA1c values. These findings suggest that iron deficiency-related microcytic anemia may lead to spuriously elevated HbA1c levels and potential misclassification of glycemic status. Therefore, hematological parameters should be considered while interpreting HbA1c values in individuals with microcytic anemia.

Limitations

The present study was conducted at a single tertiary care center with a relatively small sample size. Iron studies and serum ferritin estimation were not available for all participants. The case-control design limits causal inference regarding the relationship between microcytic anemia and HbA1c levels.

Ethical Approval

The study was conducted after obtaining approval from the Institutional Ethics Committee of Guntur Medical College and General Hospital, Guntur. Written informed consent was obtained from all participants included in the study.

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