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EFFECT OF IRON DEFICIENCY ANEMIA ON HbA1c LEVELS IN DIABETIC PATIENTS AT TERTIARY CARE CENTRE.

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Abstract:

Introduction: HbA1c, or glycated hemoglobin, is crucial for diagnosing and monitoring diabetes, reflecting average blood glucose levels over 2-3 months. However, its accuracy can be affected by conditions like iron deficiency anemia (IDA), which alters red blood cell lifespan and potentially skews HbA1c readings. This study aims to explore the effect of IDA on HbA1c levels in type 2 diabetes mellitus (T2DM) patients.

Aim: This study aims to explore the effect of IDA on HbA1c levels in type 2 diabetes mellitus (T2DM) patients

Methods: This comparative cross-sectional study was conducted from January to April 2024 at SMS Multispecialty Hospital, Ahmedabad. The study included 176 T2DM patients, divided into those with and without IDA. Data were collected through structured questionnaires and clinical examinations, including blood tests for HbA1c and various hematological parameters. Statistical analyses were performed using SPSS version 21.

Results: The IDA group exhibited significantly lower HbA1c levels (6.17 ± 1.58%) compared to the non-IDA group (7.75 ± 1.82%) with $p < 0.05$. Hematological parameters such as RBC, Hgb, HCT, MCV, MCH, and MCHC were also significantly lower in the IDA group. No significant correlation was found between HbA1c and RBC parameters in IDA patients. The distribution of anemia severity in IDA patients was 29.55% mild, 45.45% moderate, and 25.00% severe.

Discussion: The findings indicate that HbA1c levels are significantly lower in T2DM patients with IDA, potentially leading to underestimation of glycemic control. This aligns with some previous studies but contradicts others. The lack of significant correlation between HbA1c and RBC parameters suggests that HbA1c may not reliably reflect glycemic control in the presence of IDA. Healthcare providers should consider treating IDA before relying on HbA1c for diabetes management. Further research is needed to confirm these findings and explore alternative monitoring methods.

Keywords: HbA1c (Glycosylated Hemoglobin), Iron deficiency Anemia (IDA), Type 2 Diabetes Mellitus, Diabetes Management.

Introduction

HbA1c, also known as glycated hemoglobin, is a type of hemoglobin that bonds with glucose. This test is crucial for identifying the average blood sugar levels over a span of 2 to 3 months. [1] It is commonly used for diagnosing and monitoring diabetes. The HbA1c levels are categorized as follows: A level below 5.7% is normal. A level between 5.7% and 6.4% indicates prediabetes. A level of 6.5% or higher suggests diabetes. [2] This test provides a more comprehensive picture of blood glucose levels over time compared to daily [3].
The human body contains several types of hemoglobin, each with distinct functions:

1. Hemoglobin A (HbA): The predominant form in adults, making up approximately 95-98% of hemoglobin. It is composed of two alpha and two beta chains.

2. Hemoglobin A2 (HbA2): This type makes up about 2-3% of adult hemoglobin and consists of two alpha and two delta chains.

3. Hemoglobin F (HbF): The main type during fetal development, which is gradually replaced by HbA after birth. It includes two alpha and two gamma chains.

4. Hemoglobin S (HbS): Found in individuals with sickle cell disease, resulting from a mutation in the beta chain.

5. Hemoglobin C (HbC): This variant, due to a mutation in the beta chain, can cause mild hemolytic anemia.

6. Hemoglobin E (HbE): Common in Southeast Asia, this variant can cause mild anemia when inherited.

These types of hemoglobin are essential for oxygen transport and are critical indicators in various blood-related conditions. [4,5]

Hemoglobin A (HbA) becomes HbA1c through a process where glucose molecules in the blood bind to hemoglobin. This binding occurs non-enzymatically and attaches glucose to the hemoglobin molecule, forming glycated hemoglobin or HbA1c [6]

HbA1c levels are crucial for evaluating diabetes management and understanding the risk of complications. Higher HbA1c levels are linked to a greater likelihood of developing both microvascular and macrovascular complications.

1. Microvascular Complications: Elevated HbA1c levels are associated with a higher risk of damage to small blood vessels, which can lead to complications such as diabetic retinopathy (eye damage), nephropathy (kidney damage), and neuropathy (nerve damage). Persistent high HbA1c suggests poor long-term blood glucose control, which exacerbates these conditions.

2. Macrovascular Complications: High HbA1c levels are also related to an increased risk of larger blood vessel problems, including coronary artery disease, stroke, and peripheral artery disease. Long-term elevated blood glucose contributes to the development of atherosclerosis (arterial hardening), increasing the risk of these diseases.

3. Management Goals: Keeping HbA1c within target levels, generally below 7% for many individuals with diabetes, is important for reducing the risk of these complications. Regular monitoring and managing HbA1c levels can help in preventing or mitigating such health issues. [7,8]

Anemia can lead to inaccurately low HbA1c levels due to various effects on red blood cells. In conditions where red blood cells have a shorter lifespan, such as in anemia, there is less time for glucose to bind to hemoglobin. This results in lower measured levels of HbA1c. [9] Specific types of anemia, including iron deficiency anemia, hemolytic anemia, and sickle cell anemia, can further distort HbA1c readings by altering the red blood cell characteristics or increasing their turnover rates. For accurate glycemic monitoring in patients with anemia, alternative methods such as continuous glucose monitoring or fructosamine testing may be used to better reflect blood glucose control. [10]

Iron deficiency anemia occurs when there isn't enough iron in the body to produce adequate hemoglobin, the protein in red blood cells responsible for carrying oxygen. This condition can arise from several factors:

1. Causes:
   - Low Iron Intake: Insufficient dietary iron.
   - Blood Loss: Includes heavy menstrual bleeding, gastrointestinal bleeding, or other forms of blood loss.
   - Increased Demand: Situations like pregnancy or rapid growth periods.
   - Impaired Absorption: Conditions that affect the gut, such as celiac disease or Crohn's disease.

2. Symptoms:

Individuals may experience fatigue, weakness, pale skin, shortness of breath, dizziness, and headaches. In severe cases, more serious complications might arise, including heart-related issues.

3. Diagnosis: Typically involves:
   - Complete Blood Count (CBC): To measure hemoglobin and hematocrit levels.
   - Serum Ferritin: To assess the body's iron reserves.
   - Serum Iron and Total Iron-Binding Capacity (TIBC): To evaluate iron levels and the blood's capacity to transport iron.

4. Treatment: Generally, includes:
   - Iron Supplements: Taken orally or through intravenous methods in severe cases.
   - Dietary Adjustments: Consuming more iron-rich foods like red meat, beans, lentils, and fortified cereals.
   - Treating Underlying Issues: Addressing any conditions that may be contributing to blood loss or poor iron absorption [11,12]

Iron deficiency anemia is highly prevalent in India. According to the National Family Health Survey (NFHS-5) conducted between 2019 and 2021, about 59.2% of children aged 6-59 months and 53.0% of women aged 15-49 years are affected by anemia. [13]

Iron deficiency anemia can impact HbA1c measurements in the following ways:

1. Lower HbA1c Levels: In iron deficiency anemia, the reduced lifespan of red blood cells can result in falsely low HbA1c levels. Since HbA1c reflects glucose binding over the lifespan of red blood cells, a shorter lifespan means there is less time for glucose to bind, leading to lower readings.

2. Impact of Treatment: As treatment for iron deficiency anemia progresses and red blood cell turnover normalizes, HbA1c levels may increase, potentially correcting previously low readings.

3. Alternative Monitoring: Because HbA1c might not accurately represent long-term blood glucose control in individuals with iron deficiency anemia, other methods such as fructosamine testing or continuous glucose monitoring may provide a more accurate assessment. [14,15]

Anemia is under recognized and largely untreated in patients with diabetes, in Ahmedabad. We have planned to investigate the effect of IDA on HbA1c in diabetic patients attending SMS Multi-specialty hospital. Ahmedabad.

Aim:

This study aims to explore the effect of IDA on HbA1c levels in type 2 diabetes mellitus (T2DM) patients

Methods:

Study area and study population:
Study population: consisted of type 2 Diabetes Mellitus patients with Iron Deficiency Anemia attending outpatient department and those admitted to the Medicine department at Smt. SMS Multispecialty hospital, Chandkheda. Ahmedabad.

Inclusion Criteria:

Male and Female patients of aged 18 years and above.
Known case of type 2 diabetes mellitus according to the latest ADA guidelines.

Exclusion criteria:

Patients under 18 years of age
Gestational Diabetes Patients
Patients with diagnosed malignancies
Patients who refused to give consent.

Study duration: Study was conducted from January 2024 to April 2024.

Study design: Facility based Comparative cross-sectional study design
was implemented.

Diagnostic Criteria:

Latest ADA [American Diabetes Association] Guidelines for Diagnosis of Diabetes Mellitus [DM]:
Haemoglobin A1C Level ≥6.5% /
Fasting Plasma Glucose Levels ≥126 mg/dL /
2-hour Post Meal Glucose Levels ≥200 mg/dL [during OGTT] /
In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a Random Plasma Glucose Levels ≥200 mg/dL.

Questionnaire and clinical examination:

Socio-demographic data were collected using structured questionnaires. Each participant completed an enrollment form that detailed past medical history related to chronic diseases, such as kidney disease, heart problems, skin diseases, blood coagulation disorders, and other medical complaints. All participants provided a detailed medical history and underwent a physical examination. Blood tests were performed to measure levels of hemoglobin, mean corpuscular hemoglobin (MCH), hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), platelet count, total leukocyte count (TLC), differential leukocyte count (DLC), Peripheral smear examination, Glycated Hb (HbA1c), S. Iron, S. Ferritin and TIBC levels.

Questionnaire Validation:

A one-day orientation session was conducted for data collectors and supervisors to explain the study's objectives, questionnaire contents, confidentiality issues, respondents' rights, and data collection procedures. To ensure the clarity and validity of the questionnaire, a pretest was conducted with 5% of the sample size Hospital before the actual data collection began. Participants in the pretest were asked about the clarity of the questions, and data collectors provided feedback on any difficulties encountered during the process. Based on this feedback, modifications were made to the questionnaire.

Specimen Collection and Laboratory Processing:

The study included diabetic patients with and without iron deficiency anemia (IDA) who met the inclusion criteria during their hospital visit. Venous blood samples (5 mL) were collected aseptically using a needle and syringe and placed in appropriate vacutainers. Above mentioned laboratory tests were performed on collected samples.

Data Analysis

The data was initially entered into Microsoft Excel and then exported to SPSS version 21 for analysis. Frequency and summary statistics were utilized to describe the age and sex distribution among the IDA and control groups. Pearson's Chi-square test was employed to assess the association between hematological parameters and HbA1c levels. An independent t-test was conducted to compare the mean hematological parameters and HbA1c between diabetic patients with and without IDA. A p-value of less than 0.05 was considered statistically significant.

Results

The study included 176 diabetic patients, divided evenly between those with Iron Deficiency Anemia (IDA) and those without. In terms of gender, males made up 51.14% (90) of the total participants, while females comprised 48.86% (86). The average age of the participants was 47.5 years, with a standard deviation of 15.8 years.

Among the 88 patients with IDA, 61.36% (54) were male, and 38.64% (34) were female. In contrast, the non-IDA group consisted of 59.1% (52) females and 40.9% (36) males. **(Table 1)**

Table 1: Age group and sex distribution among the study population at SMS Multispecialty Hospital, Ahmedabad during January 2024 to April 2024.

Variable	IDA Group (%)	Non-IDA Group (%)	Total
Sex			
MALE	54(61.36%)	36(40.9%)	90
FEMALE	34(38.64%)	52(59.1%)	86
Age Group (years)			
18-27	12(13.64%)	9(10.23%)	21
28-37	22(25%)	11(12.5%)	33
38-47	13(14.77%)	17(19.32%)	30
48-57	11(12.5%)	22(25%)	33
58-67	20(22.73%)	19(21.60%)	39
>68	10(11.36%)	10(11.36%)	20
Total	88	88	176

Comparison of HbA1c and hematological parameters

Hematological parameters, serum ferritin, and HbA1c levels were evaluated in both the IDA and non-IDA groups. The mean and standard deviation (SD) were calculated for each parameter, and an independent t-test was conducted to compare the means of RBC, hemoglobin (Hgb), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and HbA1c between the two groups.

The results showed that the IDA group had significantly lower mean values for RBC, Hgb, HCT, MCV, MCH, MCHC, and HbA1c compared to the non-IDA group, with p-values less than 0.05 (Table 2).

Table 2: independent t test for hematological parameters among the IDA and Non-IDA groups at SMS Multispecialty Hospital, Ahmedabad during January 2024 to April 2024.

Parameters	IDA	Non-IDA	t-test P value	lower	Upper
RBC	3.44±0.80	4.92±.39	0.000	-1.650	-1.270
Hgb	9.96±2.05	15.18±1.22	0.000	-5.701	-4.700
HCT	30.42±6.38	45.3±3.55	0.000	-16.400	-13.313
MCV	88.4±8.57	92.1±3.77	0.001	-5.540	-1.580
MCH	29.9±4.02	30.95±1.60	0.027	-1.968	-0.122
MCHC	33.0±2.20	33.60±0.96	0.022	-1.110	-1.090
RDW	19.09±4.24	14.40±1.64	0.000	3.720	5.630
HbA1c	6.17±1.58	7.75±1.82	0.000	-2.060	-1.042

An analysis of the association between red blood cell (RBC) parameters and HbA1C levels was conducted in IDA patients. The mean values for RBC, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width (RDW) were calculated as 3.44±0.80, 88.4±8.57, 29.9±4.02, 33.0±2.20, and 19.09 ± 4.24, respectively.

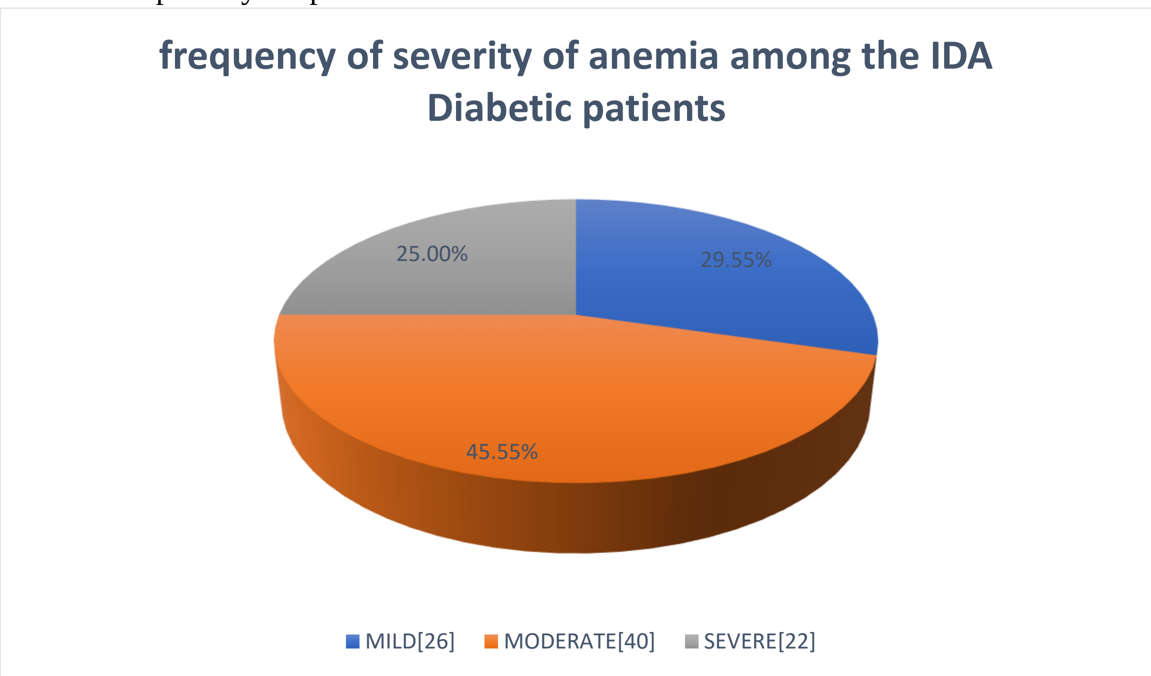
A Pearson correlation test was performed to examine the relationship between HbA1C and RBC parameters. The results showed no statistically significant correlation between HbA1C and RBC, MCV, MCH, or MCHC ($p > 0.05$) **(Table 3).**

Table 3: Association between red blood cell (RBC) parameters and HbA1C levels.

Parameters	Mean	HbA1c	
		Pearson Correlation r value	P value
RBC	3.44±0.80	-0.10	0.32
MCV	88.4±8.57	-0.28	0.78
MCH	29.9±4.02	-0.08	0.40
MCHC	33.0±2.20	-0.072	0.49
RDW	19.09±4.24	-0.10	0.35

An assessment of anemia severity was conducted in the 88 IDA patients with diabetes. The distribution of anemia severity revealed that 26 patients (29.55%) had mild anemia, 40 patients (45.45%) had moderate anemia, and 22 patients (25.00%) had severe anemia **(Figure 1)**

Figure 1: Frequency of severity of Anemia among the iron deficiency anemia patients at SMS Multispecialty hospital.



Discussion

HbA1c has gained recognition as a valuable indicator of glycemic control, glycemic risk, and predictor of diabetic complications, as well as a screening tool for diabetes diagnosis. [16] However, anemia can impact HbA1c values, either increasing or decreasing them, due to alterations in red blood cell lifespan. [17] Research has yielded varying results regarding the impact of iron deficiency anemia on HbA1c levels in both diabetic and non-diabetic patients, highlighting the need for further investigation.

The current study found a significant decrease in HbA1c levels (%) in the IDA group (6.18 ± 1.57) compared to the control group (7.74 ± 1.81) ($p < 0.05$). This finding is consistent with previous research by Sinha et al. (2012) and Cavagnolli et al. (2015), which also reported lower HbA1c concentrations in individuals with iron deficiency anemia. According to Sinha et al., the reduced HbA1c levels may be attributed to the severity of anemia in the study participants. However, conflicting results have been reported by Ford et al. (2011), Silva et al. (2015) and Chhabra et al. (2015), who found higher HbA1c levels in IDA patients.

The analysis of the association between RBC, red cell indices, and HbA1c in the IDA group revealed no statistically significant correlation. Similarly, a study conducted in India in 2014 found no significant correlation, although a borderline significant association was observed between MCH and HbA1c in IDA diabetic patients ($P = 0.05$). The comparison of hematological parameters between the two groups showed statistically significant mean differences in RBC, Hgb, MCV, and MCH, consistent with a study conducted in India in 2016.

The classification of iron-deficient patients based on hemoglobin levels revealed that 26 patients (29.55%) had mild anemia, 40 patients (45.45%) had moderate anemia, and 22 patients (25.00%) had severe anemia. The current study found no significant association between sex, age, and HbA1c in IDA diabetic patients, aligning with the findings of a similar study conducted in India.

Conclusion

In summary, this study reveals that individuals with iron deficiency anemia (IDA) tend to have significantly lower HbA1c levels compared to those without IDA. This discrepancy may lead to inaccurate assessments of glycemic control when relying solely on HbA1c measurements. Therefore, healthcare providers should exercise caution when interpreting HbA1c results in patients with IDA, recognizing that the actual values may be falsely lowered. It is recommended that iron deficiency anemia be addressed and treated before diagnosing and managing diabetes using HbA1c. Further research with a larger participant pool and advanced laboratory techniques is warranted to confirm these findings.

Abbreviations

RBC (Red blood cells), Hgb (Hemoglobin), HCT (Hematocrit), MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Hemoglobin), MCHC (Mean Corpuscular Hemoglobin concentration), and HbA1c (Glycosylated Hemoglobin).

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