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Research Article

Relationship Between Hba1c AndSerum Iron And Transferrin Saturation In Iron-Deficiency Non-Diabetic Patients

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ABSTRACT

Objective: To determine if iron deficiency(ID) should be considered before making any treatment decisions based only on glycosylated hemoglobin (HbA1c) values, and to assess the effect of ID on theHbA1clevels of non-diabetic persons.

Methods: Between September 2023 and March 2024, a cross-sectional comparison study was carried out at the Index Medical College Hospital and Research Centre in Indore on non-diabetic patients based on fasting blood sugar of <100 mg/dl.There were two groups of patients. Patients with ID anemiawere included in group-1, while healthy people who were age and sex matched but did not have ID were included in group-2. A sample of blood was drawnfor serum iron, total iron binding capacity, CBC, and HbA1c. TSAT, or transferrin saturation, was computed. Student's t-test was used to compare quantitative variables between the group1 and group 2. Given that the data was not normally distributed, a correlation between HbA1c and iron and TSAT was performed in both groups using the Kendal tau-b test.

Results:Among the 198 patients, 83 (41.9%) men and 115 (59.1%) women. With a p-value <.001, the ID group's mean HbA1c level was considerably higher (5.88±0.43) than that of the non-ID group (5.51±0.48). Serum iron levels, transferrin saturation, and hemoglobin all showed a negative correlation with the HbA1c values. P-value less than.001.

Conclusion: Reduced serum Iron and TSAT was associated with increased HbA1c value. Prior to interpreting the HbA1c, an iron deficit must be treated.

Keywords: iron deficiency anemia, HbA1c in iron deficiency, serum transferrin

INTRODUCTION

A slightly more severe form of iron shortage is known as iron deficiency without anemia, which is typified by the absence of stored iron, often low blood iron content, and transferrin saturation, but not by overt anemia. Iron deficiency is the most prevalent deficiency disorder globally, according to the WHO. In India, iron deficiency anemia is also the most prevalent type. A decreased erythrocyte lifetime, particularly as a result ofanemia, is one important aspect considered to be a confounding factor in the use of HbA1c[1].

The essential form of glycosylated hemoglobin is hemoglobin A1C (HbA1c).Serum glucose and the N-terminal amino acid of hemoglobin's β-chain react to create it through the ketamine reaction. The ratio of glycosylated haemoglobin to average plasma glucose levels is proportional. The plasma glucose levels during the previous three months are reflected in the HbA1c of diabetes patients[2].HbA1c was previously thought to be solely influenced by plasma glucose levels, but more recent research has revealed that a wide range of factors, including hemoglobinopathies, hemolyticanemias, chronic kidney disease, alcoholism, pregnancy, and dietary anemias, can affect its levels in addition to diabetes[3].

Deficiency of iron is one of the most common types of malnutrition. An iron deficiency (ID) is thought to be the cause of 50% of anemia worldwide. ID can be objectively estimated using a variety of laboratory markers, including hemoglobin with peripheral smear, serum iron levels, transferrin saturation, total iron binding capacity, and serum ferritin levels[4]. Iron is stored as ferritin, which is a reliable indicator of iron status. Previous research has demonstrated a connection between decreased ferritin levels and elevated HbA1c, which can cause diabetics to have falsely high HbA1c values[5].
Research has indicated that a drop in iron levels causes an increase in HbA1c glycation.The following are alternative theories behind the elevated HbA1c level in ID[2]:
• A faster rate of globin chain glycation as a result of the quaternary structural alteration.
• The generation of red blood cells decreases in iron deficiency anemia, extending the life of red blood cells and raising the HbA1c level.
• The glycation of hemoglobin increases as a result ofhemoglobin's decreased level, raising HbA1c levels.

Recent research by Sinha et al. demonstrated that when iron deficiency anemia(IDA) was treated, both absolute and HbA1c levels rose[6]. The choice was made to investigate the impact of IDA on HbA1c levels in adult Indians who are not diabetics due to the contradictory findings of all this research. Anemia with hypochromic microcytic anemia is caused by iron insufficiency. Ferritin and hemosiderin reserves may be sufficient to sustain normal hemoglobin and hematocrit levels, as well as normal serum iron and transferrin saturation, at the onset of chronic blood loss or other conditions of negative iron balance. Without causing anemia, the gradual depletion of these stores initially reduces serum iron and transferrin saturation levels. Erythroid activity in the bone marrow is elevated in this early stage. Anemia appears only when iron stores are completely depleted and is accompanied by low serum iron, ferritin, and transferrin[7].
Since an individual's HbA1c levels reflect their glycemic control, it is crucial to rule out variables that could mistakenly raise them. Previous research has suggested that IDA influences HbA1c levels, but the findings were inconsistent[2]. Son NE et al. used serum ferritin levels as a marker for iron deficiency to correlate with HbA1c[8]. Similarly, Son NE reported increased serum ferritin levels with rising HbA1c levels in patients with type 2 DM, although its findings may be invalid due to ferritin's acute phase reactant properties[8]. It was estimated that about 50 to 70 percent of reproductive women are anemic in India[9, 10]The purpose of this study was to evaluate the impact of ID on non-diabetic individuals' HbA1c levels and to ascertain if ID should be taken into account before making any treatment decisions based just on HbA1c values.

MATERIAL AND METHODS

Between September 2023 and March 2024, a cross-sectional comparison study was carried out at the Index Medical College Hospital and Research Centre in Indore. The institutional ethics review board committee granted ethical approval. Every patient provided written, informed consent. Based on blood iron and transferrin saturation, all non-diabetic patients between the ages of 18 and 65 were included and divided into two groups. Individuals without a known history of diabetes and with fasting blood sugar (FBS) levels less than 100 mg/dl were classified as non-diabetics[11], whereas those with serum iron levels less than 60 µg/dl and serum transferrin saturation less than 20% were classified as iron deficient[12].Patients who had serum iron levels below 60µg/dl and transferrin saturation levels below 20% were placed in Group-1, while those who had serum iron levels beyond 60µg/dl and transferrin saturation levels over 20% were placed in Group-2.

Inclusion and exclusion criteria

Individuals having a past medical history of hemolyticanemia, hemoglobinopathies, acute blood loss, chronic kidney illness, alcohol consumption, vitamin B12, and folate deficits were not accepted. Individuals using medications such as corticosteroids, antiretrovirals, ribavirin, etc. that potentially alter HbA1c values were also disqualified.

Sample size determination

Using a two-sided hypothesis test with a significance threshold of 0.05, the sample size was determined with a power of 0.90 to detect a difference of -0.26 between the null hypothesis correlation of <0.001 and the alternative hypothesis correlation of 0.26.[13] Based on the above characteristics, 158 was determined to be the sample size.
Patients who met the screening criteria but were not diabetics were admitted with their informed written agreement. Specific demographic information was noted. A 10-milliliter venous sample was obtained to measure serum iron, total iron binding capacity (TIBC), complete blood count, and HbA1c. Transferrin saturation was computed using the following formula. TIBC (µg/dL) x 100 / serum iron level (µg/dL) equals transferrin saturation (%). Using a Bio-Rad D10 analyzer, the HPLC method was used to assess serum iron and HbA1c. Patients were told to report for plasma glucose estimation using the oxidase/peroxidase technique after eight hours of fasting. According to the operational definition, patients with iron deficit were assigned to Group-1, while patients without ID were assigned to Group-2.

Data analysis

The x2 test was used to compare the frequencies of qualitative factors such as gender and ID status. The means ±SD of several quantitative variables, including age, transferrin saturation, iron, and HbA1c, were calculated. The t-test was used to compare the quantitative factors of age, HbA1c, iron & transferrin saturation with the ID Groups and gender. The Kolmogorov-Smirnov (KS) Test was used to verify that all quantitative variables had a normal distribution. Since the KS Test result was less than 0.05, the data was not normally distributed. Thus, Kendall's Tau-b test was used to correlate HbA1c with transferrin saturation and iron. With a significance level of ≤0.05. IBM SPSS for windows (version 20.0; SPSS Inc. Chicago, IL, USA) software was employed to analyze the data.

RESULTS

Following informed permission, 198 patients in total were enrolled in the trial. There were 83 (41.9%) men and 115 (59.1%) women. The average age of the males and females was 42.7 ± 14.7 years and 45.9 ± 12.3years, respectively. Age and HbA1c did not significantly differ between the sexes. Hemoglobin, serum iron, and transferrin saturation were found to differ significantly by gender; specifics are displayed in Table I.Age-wise, there was no discernible difference between Groups 1 and 2 (t (196) = -1.916, p = 0.058). But there was a noticeable difference in the levels of hemoglobin, serum iron, and HbA1c. With a p-value of less than.001, Group-1's mean HbA1c level was significantly higher (5.88 ± 0.43) than Group-2's (5.51 ± 0.48). Table-II provides details on it. The non-parametric Kendall's tau-b test was used to examine the connection between blood iron and hemoglobin with HbA1c because the data was not regularly distributed. Serum iron levels, transferrin saturation, and hemoglobin all showed a negative correlation with the HbA1c values. which are detailed in Table III.

Table-I: Comparison of quantitative variables with gender by Student's t-test

	Gender	Mean ±SD	Sig.	95% CI for Mean	
				Upper	Lower
Age (years)	Female	42.7 ± 14.7	0.195	1.152	-6.009
	Male	45.9 ± 12.3			
Hemoglobin (gm/dl)	Female	9.95±1.97	0.41*	0.456	0.668
	Male	11.01±2.23			
HbA1c	Female	5.75±0.51	0.359	0.072	-0.199
	Male	5.79±0.42			
Serum Iron (µg /dl)	Female	45.42±22.9	0.035*	5.937	7.008
	Male	50.98±25.78			
Transferrin saturation (%)	Female	29.15±9.98	0.038*	29.042	12.103
	Male	35.47±12.27			

Table-II: Comparison of age, HbA1c, serum iron & transferrin saturation with ID Groups by Student's t-test.

	Groups	Mean ±SD	Sig.	95% CI for Mean	
				Upper	Lower
Age (years)	Group 1	45.12±13.16	0.58	0.102	-6.902
	Group 2	41.72±13.22			
HbA1c	Group 1	5.88±0.43	<0.001*	-0.256	-0.494
	Group 2	5.51±0.48			
Serum Iron (µg /dl)	Group 1	33.64±13.28	<0.001*	45.06	38.66
	Group 2	75.53±10.01			
Transferrin saturation (%)	Group 1	8.92±3.44	<0.001*	23.02	12.76
	Group 2	39.62±7.13			

*. Significant level ≤.05

Table-III: Correlation matrix of HbA1c with Hemoglobin, Serum Iron and Transferrin Saturation

		Hemoglobin (gm/dl)	Serum Iron (mcg /dl)	Transferrin saturation (%)
HbA1c	Correlation Coefficient	-0.289**	-0.285**	-0.293**
	Sig. (2-tailed)	<0.001*	<0.001*	<0.001*

*. Significant level ≤.05, **. "Correlation is significant at the .01 level (2-tailed)".

DISCUSSION

IDA, a condition that lowers iron storage and impairs erythropoiesis, the process that makes red blood cells [52]. When low hemoglobin, low serum iron, low serum ferritin, low transferrin saturation, and high TIBC are detected in a laboratory setting, IDA can be diagnosed[14, 15]. Clinically, individuals may feel weak and exhausted. In diabetes mellitus, tracking the HbA1c level is essential to the diagnostic process and subsequent assessment. HbA1c, however, may also be impacted because RBCs and hemoglobin are aberrant in IDA, according to studies. The IDA-induced RBC turnover and hemoglobin structure alterations have been proposed as potential causes of the falsely increased HbA1c values observed in IDA patients. Nevertheless, a comprehensive account of the process behind the variations in HbA1c is still lacking, necessitating additional research to validate and clarify the function of IDA[16].

Our investigation revealed two key conclusions: first, that those with iron deficiency have greater HbA1c levels than those without; and second, the saturation levels of transferrin, serum iron, and hemoglobin are strongly inversely correlated with HbA1c levels.Iron deficiency accounts for 50% of all anemias worldwide and is a common nutritional deficiency that is frequently encountered in clinical practice. Elevated HbA1c values are associated with iron insufficiency. In addition to being used to identify diabetes and pre-diabetes, or those at high risk of acquiring diabetes, HbA1c also reveals glycemic status during the three months prior. HbA1c readings are influenced by a number of factors, including age, genetics, ethnicity, and certain illnesses. Regardless of the glucose level, prior research has indicated that ID may increase the HbA1c level. Therefore, in individuals with specific anemias, blood loss, or ID, the HbA1c test may not accurately reflect glycemic status[2].

According to a study by El-Agouza L et al., patients with iron deficiency anemia had higher HbA1c levels, which considerably dropped when iron was administered[17].Recently, Sinha et al. demonstrated that when iron deficiency anemia was treated, both absolute and HbA1c levels rose[6].In his study, Intra J et al. also found that the adjusted averages of HbA1c were significantly higher in anemic persons (5.59% 37.37 mmol/mol) compared to non-anemic individuals (5.34% 34.81 mmol/mol) P<0.001)[18].Additionally, prior research has demonstrated that ID is linked to higher HbA1c readings in people with or without diabetes, which go down when ID is corrected.

In this study, we discovered a statistically significant difference in HbA1c levels between the ID and non-ID groups, with the higher levels of HbA1c inside the ID category.

According to Madhu et al., ID subjects had substantially higher HbA1c levels (5.51 ± 0.696) than the healthy control group (4.85 ± 0.461%); p <.001. In ID subjects, they found a negative correlation (r=-0.632, -0.652, -0.384, -0.236, -0.192, and -0.441) between HbA1c and hemoglobin, hematocrit, RBC count, MCH, MCHC, and serum ferritin. Following iron replacement, a significant decline in HbA1c levels was observed in ID subjects (5.51+/-0.696 before treatment v/s 5.044 ±0.603 post-treatment; p<.001). A statistically significant difference (p value <.001) was also noted by Bansal et al. (23.23) between the ID and control groups, with mean HbA1c values of 6.11 ± 0.42 and 5.01 ± 0.41, respectively[19].

In their research, Cetinkaya Altuntas S et al. found that IDA rose following iron therapy and was linked to low HbA1c levels[20].Nonetheless, patients with IDA had higher HbA1c values, according to Coban E et al. For three months, they gave the ID patients an additional 100 mg of iron per day, and they then monitored the patients' HbA1c. Following iron therapy, they discovered that the HbA1c levels dropped dramatically to 6.2% ±0.6 (p <.001)[21].

Christy et al.[22], and Bukhari et al[23]. reported findings that were comparable. Contradictory results were reported by Sinha et al[24]. (2013), with HbA1c levels in ID patients being lower than in the control group (4.6% in the ID group versus 5.5% in the control group, P<.05. In addition, they found that following two months of iron therapy, HbA1c levels significantly increased (0.29 g/dL vs. 0.73 g/dl, p <.01). While the precise cause of the elevated HbA1c levels in ID remains unknown, a small number of studies have documented this phenomenon.

LIMITATIONS

A couple of the study's drawbacks include its small sample size and lack of follow-up following iron therapy. Using participants who were not diabetics, this study is plausible that anemia may have a stronger impact on HbA1c levels, which may have important clinical implications for DM patients. The study's single site and hospital-based methodology prevented the results from being applied to the broader public.

CONCLUSION

This study provided statistical evidence for the relationship between ID and HbA1c levels. Therefore, the population with diabetes should routinely check their iron status as well, since it may have an impact on the HbA1c parameter, which is used to gauge how well they are controlling their blood sugar.

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