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Original Article

Serum Iron Markers and Their Association with HbA1c in a Non-Diabetic Population

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ABSTRACT

Introduction: *Iron metabolism plays a crucial role in various physiological processes, including oxygen transport, energy production, and enzymatic functions. Emerging evidence suggests that alterations in iron homeostasis may influence glycemic markers, even in individuals without diabetes. Therefore, this study aimed to assess the serum iron markers and their association with HbA1c in a non-diabetic population.* ***Methods & Materials:*** *This cross-sectional study was conducted at the Department of Physiology, Sir Salimullah Medical College (SSMC), Dhaka, from July 1, 2017 to July 30, 2018. A total of 48 subjects were selected by consecutive purposive sampling technique. Statistical analysis was done by SPSS version 25.0. Statistical analysis included Pearson's correlation.* ***Result:*** *Among subjects with good glycemic control, no significant correlations were found between HbA1c levels and serum iron, TIBC, ferritin, or transferrin saturation. However, hemoglobin levels showed a significant negative correlation with HbA1c ($r = -0.538$, $p < 0.01$). In contrast, among subjects with poor glycemic control, significant correlations were observed between HbA1c levels and serum iron ($r = +0.483$, $p = 0.017$), TIBC ($r = -0.560$, $p = 0.004$), ferritin ($r = +0.487$, $p = 0.016$), and transferrin saturation ($r = +0.483$, $p = 0.017$), whereas hemoglobin levels did not significantly correlate with HbA1c ($r = +0.079$, $p = 0.715$).* ***Conclusion:*** *This study explores the link between serum iron markers and HbA1c in non-diabetics, showing significant correlations in those with poor glycemic control, while only hemoglobin showed a negative correlation in those with good control.*

Keywords: *Iron Markers, HbA1c, Non-Diabetic, Ferritin*

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INTRODUCTION

Hemoglobin A1c (HbA1c) is a key biomarker for assessing long-term glycemic control and is widely used in the diagnosis and monitoring of diabetes mellitus. It reflects the average blood glucose levels over the past 8 to 12 weeks and is influenced primarily by glucose exposure to erythrocytes [1]. However, accumulating evidence suggests that non-glycemic factors, particularly iron metabolism, may influence HbA1c levels, leading to potential misinterpretations of glycemic status in individuals with altered iron homeostasis. Since HbA1c formation depends on hemoglobin glycation, conditions that affect erythrocyte turnover—such as iron deficiency anemia, iron overload, or altered iron-binding capacity—can significantly impact its values [2]. This raises concerns about the reliability of HbA1c in diagnosing and assessing glycemic control, especially in individuals with abnormal iron profiles but without diabetes. Iron plays a crucial role in oxygen transport, erythropoiesis, and various metabolic pathways. Its status is commonly assessed through serum iron, ferritin, total iron-binding capacity (TIBC), and transferrin saturation (TS) [3]. Studies have shown that iron deficiency can lead to an artificial increase in HbA1c, even in individuals with normal blood glucose levels. This occurs due to reduced erythropoiesis, leading to older red blood cells remaining in circulation longer and accumulating more glycation over time [4]. Conversely, iron overload conditions, such as hemochromatosis or frequent blood transfusions, may result in lower HbA1c levels due to increased red blood cell turnover and faster clearance of glycated hemoglobin [5]. These findings suggest that iron metabolism could be a crucial determinant of HbA1c values, independent of glucose metabolism. Several studies have explored the relationship between iron metabolism and HbA1c in diabetic and anemic populations, but limited research has focused on healthy, non-

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diabetic individuals [6]. Understanding this relationship in a non-diabetic population is essential, as it may help refine diagnostic cut-offs for prediabetes and diabetes, ensuring that HbA1c levels are interpreted accurately in individuals with varying iron statuses. Moreover, some evidence suggests that alterations in iron metabolism may be linked to insulin resistance and metabolic syndrome, potentially acting as an early metabolic disturbance before the onset of diabetes [7]. Identifying such associations in a healthy population could improve early risk stratification and preventive strategies for metabolic disorders. By analyzing iron metabolism parameters, including serum iron, ferritin, TIBC, and transferrin saturation, in relation to HbA1c, this research seeks to clarify the extent to which iron homeostasis influences glycemic markers. By studying a non-diabetic population, researchers can determine how iron metabolism independently affects HbA1c levels without the confounding impact of diabetes. So, by identifying non-glycemic factors that influence its levels, such as iron deficiency, anemia, and erythrocyte turnover. It highlights the risk of misclassification of prediabetes or diabetes due to iron-related alterations in HbA1c, aiding in more accurate clinical interpretation. Additionally, it explores whether iron-related abnormalities correlate with future diabetes risk by affecting insulin resistance. Therefore, this study aimed to assess the serum iron markers and their association with HbA1c in a non-diabetic population.

METHODS & MATERIALS

This cross-sectional study was conducted at the Department of Physiology, Sir Salimullah Medical College (SSMC), Dhaka, from July 1, 2017 to July 30, 2018. A total of 48 subjects were selected by consecutive purposive sampling technique. This study was conducted on a non-diabetic population to evaluate the association between serum iron markers and HbA1c levels. Participants were recruited based on predefined inclusion and exclusion criteria, ensuring the absence of diabetes through fasting plasma glucose (FPG) and HbA1c cutoffs. Blood samples were collected after an overnight fast to measure serum iron, ferritin, total iron-binding capacity (TIBC), transferrin saturation, and HbA1c. Standardized enzymatic and immunoturbidimetric assays were used for biochemical analysis. Statistical analysis was done by SPSS version 25.0. Statistical analysis included Pearson's correlation. Ethical approval was obtained, and informed consent was secured from all participants.

RESULTS

Table – I: Correlation of iron status with HbA1c level in good glycemic control subjects (*n*=24)

Parameters	r value	p-value
S. Iron	-0.277	0.190
TIBC	+0.144	0.502
Ferritin	-0.014	0.947
Transferrin Saturation%	-0.217	0.309
Hb	-0.538	0.007**

r value was done by Pearson's correlation

** = significant at p<0.01

In this study there was no correlation between serum iron (r = - 0.277 and p = 0.190) and HbA1c level, no correlation between serum TIBC (r = + 0.144 and p = 0.502) and HbA1c level, no correlation between serum ferritin (r = - 0.014 and p = 0.947) and HbA1c level, no correlation between transferrin saturation (r = - 0.217 and p = 0.309) and HbA1c level in good glycemic non-diabetic subjects. Moreover, hemoglobin level (r = - 0.538) was negatively correlated with HbA1c in good glycemic non-diabetic subjects. This relationship was statistically (p<0.01) significant. [Table I]

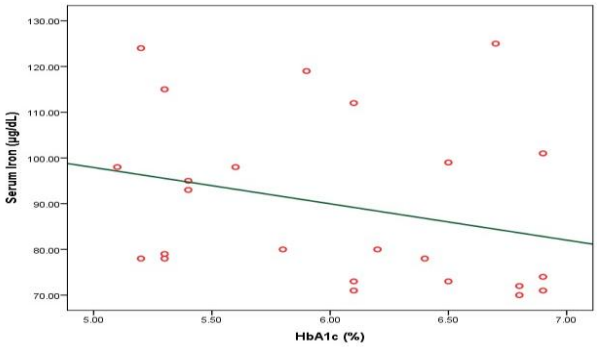

Figure – 1: Correlation of serum iron level with HbA1c level in good glycemic control subjects (*n*=24)

Pearson's correlation coefficient r = - 0.277 and p = 0.190.

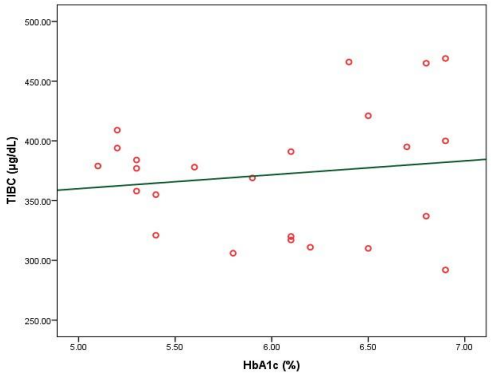

Figure – 2: Correlation of serum TIBC level with HbA1C level in good glycemic control subjects (*n*=24)

Pearson's correlation coefficient r = + 0.144 and p = 0.502.

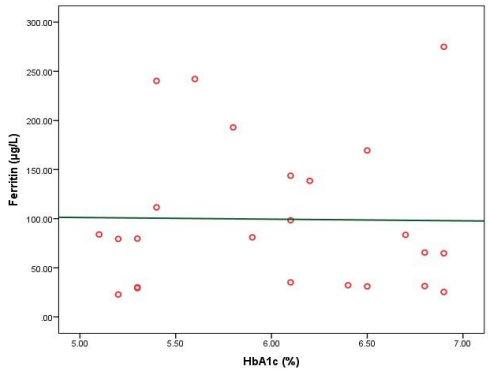

Figure – 3: Correlation of serum ferritin level with HbA1c level in good glycemic control subjects (*n*=24)

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Pearson's correlation coefficient r = - 0.014 and p = 0.947

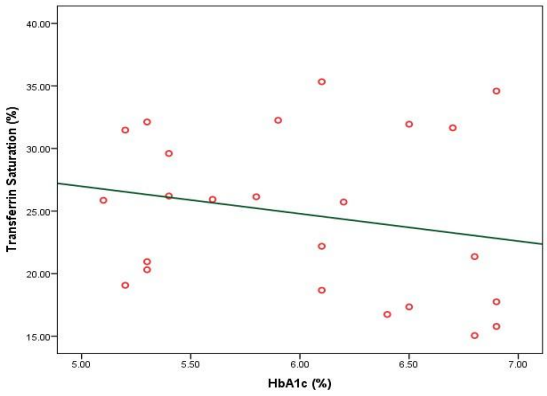

Figure – 4: Correlation of transferrin saturation level with HbA1c level in good glycemic control subjects (*n*=24)

Pearson's correlation coefficient r = - 0.217 and p = 0.309

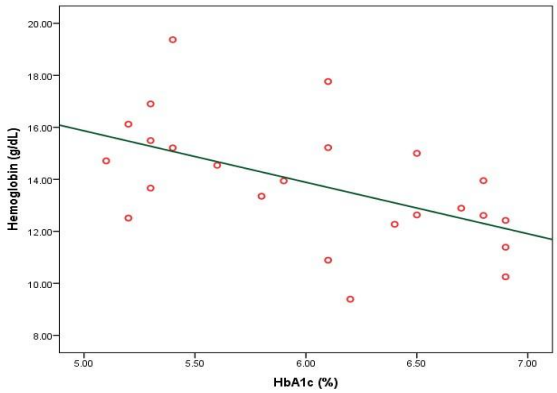

Figure – 5: Correlation of Hemoglobin level with HbA1c level in good glycemic control subjects (*n*=24)

Pearson's correlation coefficient r = - 0.538 and p = 0.007

Table – II: Correlation of iron status with HbA1c level in poor glycemic control subjects (*n*=24)

Parameters	r value	p-value
S. Iron	+0.483	0.017*
TIBC	-0.560	0.004**
Ferritin	+0.487	0.016*
Transferrin Saturation%	+0.483	0.017*
Hb	+0.079	0.715

r value was done by Pearson's correlation test, ** = significant at p<0.01, * = significant at p≤0.05

In this study, serum iron level (r = + 0.483) positively correlated with HbA1c level in poor glycemic control subjects. This relationship was statistically significant (p≤0.05). Serum TIBC level (r = - 0.560) was negatively correlated with HbA1c level in poor glycemic control subjects. This relationship was statistically (p<0.01) significant. serum ferritin level (r = + 0.487) was positively correlated with HbA1c level in poor glycemic control subjects. This relationship was statistically ((p≤0.05) significant. transferrin saturation level (r = + 0.483) positively correlated with HbA1c level in poor glycemic control subjects. This relationship was statistically (p≤0.05) significant. Hemoglobin level was positively (r = + 0.079) correlated with HbA1c level, but this relationship was not statistically significant. [Table II]

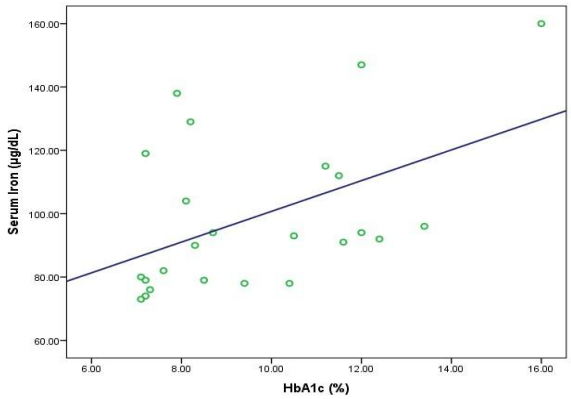

Figure – 6: Correlation of serum iron level with HbA1c level in poor glycemic control subjects (*n*=24)

Pearson's correlation coefficient r = + 0.483 and p = 0.017

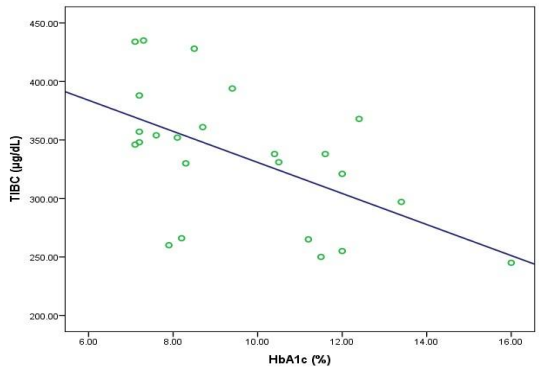

Figure – 7: Correlation of serum TIBC level with HbA1c level in poor glycemic control subjects (*n*=24)

Pearson's correlation coefficient r = - 0.560 and p = 0.004

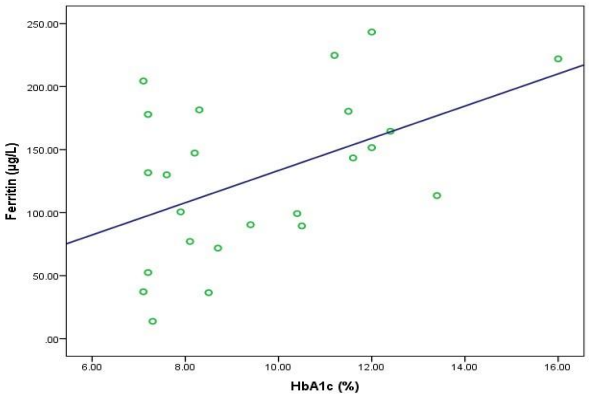

Figure – 8: Correlation of serum ferritin level with HbA1c level in poor glycemic control subjects (*n*=24)

Pearson's correlation coefficient r = + 0.487 and p = 0.016

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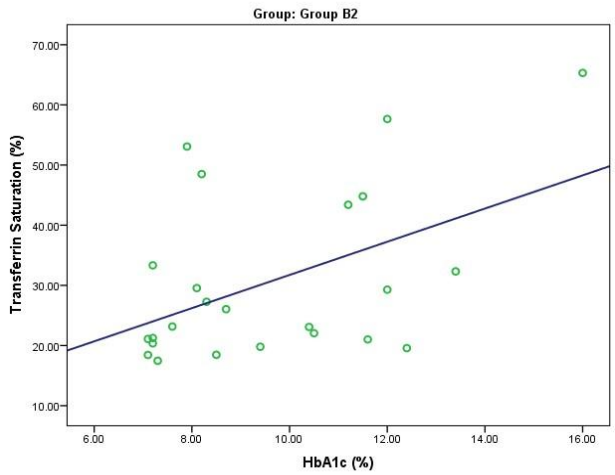

Figure – 9: Correlation of transferrin saturation level with HbA1c level in poor glycemic control subjects (*n*=24)

Pearson's correlation coefficient r=+ 0.483 and p= 0.017

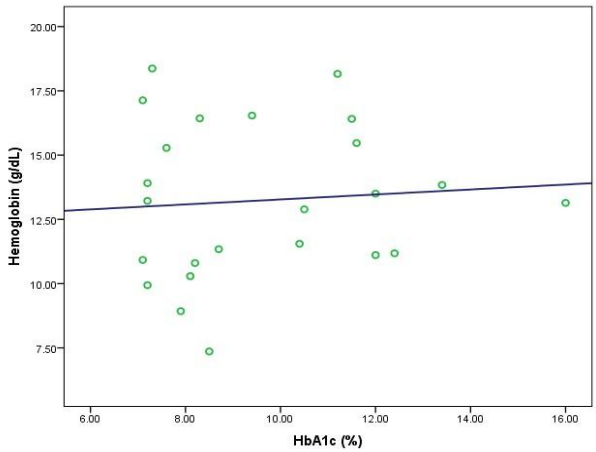

Figure – 10: Correlation of Hemoglobin level with HbA1c level in poor glycemic control subjects (*n*=24)

Pearson's correlation coefficient r = + 0.079 and p = 0.715

DISCUSSION

The findings of this study indicate a differential correlation between iron status markers and HbA1c levels in non-diabetic subjects with good and poor glycemic control. Among non-diabetic subjects with good glycemic control, no significant correlations were observed between serum iron (r = -0.277, p = 0.190), TIBC (r = +0.144, p = 0.502), ferritin (r = -0.014, p = 0.947), or transferrin saturation (r = -0.217, p = 0.309) with HbA1c levels, suggesting that in individuals with stable glycemic status, iron metabolism does not significantly influence HbA1c [4]. However, hemoglobin levels were negatively correlated with HbA1c (r = -0.538, p = 0.007), which aligns with evidence that increased erythropoiesis or higher hemoglobin turnover results in lower glycation of hemoglobin [8]. This finding is consistent with previous research, which suggests that lower hemoglobin turnover rates, often seen in anemia, lead to prolonged hemoglobin exposure to glucose, resulting in artificially elevated HbA1c levels [9]. In contrast, among non-diabetic subjects with poor glycemic control, serum iron (r = +0.483, p = 0.017), ferritin (r = +0.487, p = 0.016), and transferrin saturation (r = +0.483, p = 0.017) were positively correlated with HbA1c, while TIBC showed a significant negative correlation (r = -0.560, p = 0.004), indicating that iron overload may contribute to increased hemoglobin glycation [7]. This relationship could be explained by oxidative stress and inflammation associated with elevated iron stores, leading to enhanced glucose auto-oxidation and insulin resistance [10]. Previous studies have suggested that iron overload can promote pancreatic beta-cell dysfunction, reducing insulin secretion and contributing to impaired glucose metabolism even in non-diabetic individuals [11]. The significant negative correlation between TIBC and HbA1c in this study further supports the hypothesis that individuals with lower TIBC, which is indicative of higher iron stores, tend to have elevated HbA1c levels [12]. Iron metabolism is intricately linked to glucose homeostasis, as iron plays a crucial role in mitochondrial function and insulin signaling [13]. Disruptions in iron balance, whether in the form of deficiency or excess, can influence glycation processes and glycemic markers [14]. Several studies have reported that increased ferritin levels are associated with higher HbA1c, even in the absence of diabetes, due to ferritin's role as an acute-phase reactant that reflects chronic inflammation [15]. Chronic inflammation and oxidative stress associated with elevated iron stores can accelerate non-enzymatic glycation of hemoglobin, thereby increasing HbA1c levels independently of glucose concentrations. Additionally, excess iron can impair insulin action through the production of reactive oxygen species, leading to insulin resistance and compensatory hyperinsulinemia, further affecting glucose metabolism [16]. This study supports these findings, demonstrating that individuals with poor glycemic control had higher ferritin levels, which correlated positively with HbA1c, whereas no such relationship was found in those with good glycemic control [17]. The hemoglobin levels in the poor glycemic control group (r = +0.079, p = 0.715) did not show a significant correlation with HbA1c, suggesting that in those with poor glycemic control, factors beyond hemoglobin concentration, such as metabolic alterations and oxidative stress, may play a larger role in influencing HbA1c levels [18]. This contrasts with findings in diabetic populations, where hemoglobin levels and erythrocyte turnover have been shown to significantly influence HbA1c variability [19]. These findings emphasize the need to consider iron status when interpreting HbA1c levels in non-diabetic individuals, as iron deficiency anemia can falsely elevate HbA1c, while iron overload may lead to an underestimation of glycemic status.

Limitations of The Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

CONCLUSION

This study highlights the association between serum iron markers and HbA1c levels in a non-diabetic population, providing insights into how iron metabolism may influence

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glycemic markers independent of diabetes. The findings reveal significant correlations between serum iron, ferritin, transferrin saturation, and total iron-binding capacity (TIBC) with HbA1c in individuals with poor glycemic control, whereas no significant associations were observed in those with good glycemic control, except for hemoglobin, which showed a negative correlation. These results suggest that alterations in iron status may impact HbA1c levels even in non-diabetic individuals, potentially influencing its reliability as a glycemic marker.

RECOMMENDATION

Based on the findings of this study, it is recommended that clinicians consider iron status when interpreting HbA1c levels in non-diabetic individuals, as variations in serum iron markers may influence glycemic assessments. Future research should focus on larger population-based studies to further validate these associations and explore the potential impact of iron metabolism on HbA1c reliability.

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