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Serum Iron and HbA1c in Complicated and Uncomplicated Diabetes Mellitus Patients: A Comparative Study

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ABSTRACT

Background: Diabetes mellitus (DM) is a chronic disorder linked with significant metabolic disturbances and risk of complications. Glycated hemoglobin (HbA1c) reflects long-term glycemic control, while serum iron alterations may contribute to oxidative stress and diabetic complications. This study aimed to compare serum iron and HbA1c levels in diabetes mellitus patients with and without complications.

Method: This prospective comparative study included 40 type 2 diabetes mellitus patients at a tertiary care center, divided into two groups: Group A (20 patients without complications) and Group B (20 patients with one or more complications, such as nephropathy, neuropathy, retinopathy, or cardiovascular disease). Demographic data, serum iron (colorimetric method), and HbA1c (HPLC) were assessed.

Result: The mean age in Group A was 53.46 ± 8.22 years and in Group B was 56.13 ± 7.55 years ($p>0.05$). Male-to-female ratio was 11:9 in Group A and 12:8 in Group B. Mean duration of diabetes was longer in Group B (9.87 ± 4.13 years) compared to Group A (5.74 ± 3.66 years) ($p=0.0019$*). Mean HbA1c was significantly higher in Group B (9.17 ± 1.33%) versus Group A (7.43 ± 1.20%) ($p<0.001$). Mean serum iron was lower in Group B (62.51 ± 17.62 µg/dL) compared to Group A (84.25 ± 14.84 µg/dL) ($p<0.001$*). A moderate negative correlation was observed between HbA1c and serum iron in complicated DM patients ($r = -0.48$, $p=0.016$*).

Conclusion: Patients with complicated diabetes mellitus exhibited poorer glycemic control and lower serum iron levels compared to uncomplicated DM patients. A negative association between HbA1c and serum iron highlights the potential role of iron metabolism in the progression of diabetic complications.

Keywords: Diabetes Mellitus Type 2; Hemoglobin A, Glycosylated; Iron; Anemia, IronDeficiency; Diabetic Complications; Serum Iron

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) has emerged as a major public-health challenge worldwide, with rapidly rising prevalence and a significant burden of microvascular and macrovascular complications. Effective glycaemic control is pivotal in slowing or preventing these complications, and glycated haemoglobin (HbA1c) has become a cornerstone measure of longterm glycaemia in routine clinical practice. However, emerging evidence suggests that alongside glucose metabolism, micronutrient factors—particularly iron status—play an influential role in modulating both metabolic control and the development of diabetic complications.

Iron is a vital micronutrient with key roles in oxygen transport, mitochondrial function, and redox biology. At the same time, iron metabolism has been implicated in pathways relevant to insulin secretion, insulin sensitivity and oxidative stress. For instance, body iron overload has been linked to β cell dysfunction, hepatic gluconeogenesis and insulin resistance, thereby increasing the risk of incident T2DM. [1] On the other end of the spectrum, iron deficiency (ID) and iron-deficiency anaemia (IDA) appear to perturb glucose homeostasis, impairing insulin action and possibly enhancing glycaemic variability. [2] In this dual context, iron metabolism emerges as a biologically plausible modulator of both glycaemic control and diabetes complications.

In patients with diabetes, the interplay between HbA1c and iron status is gaining interest. Iron deficiency and anaemia have been shown to elevate HbA1c values independent of actual glycaemic exposure, likely through altered erythrocyte turnover and increased glycation of haemoglobin. [3-5] This raises two clinically relevant concerns: firstly, that HbA1c may be over- or under-estimated in the presence of iron abnormalities; and secondly, that impaired iron homeostasis may itself be linked to worse glycaemic control and more frequent complications.

Complications of diabetes such as nephropathy, retinopathy, neuropathy and cardiovascular disease are closely related to the duration of diabetes and quality of glycaemic control. Given the plausible mechanistic links between iron metabolism, glycaemia and oxidative damage, it is reasonable to hypothesize that patients with diabetic complications might display distinct iron profiles compared to those without complications. Despite this potential, few studies have directly compared iron parameters between patients with and without diabetic complications, while simultaneously examining their correlation with HbA1c levels.

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In light of this gap, our prospective comparative study aimed to evaluate and compare serum iron and HbA1c values in patients with uncomplicated T2DM versus those with established complications. Additionally, we sought to assess the correlation between HbA1c and serum iron levels within each group. Understanding these associations may provide further insight into whether iron status should be considered in the comprehensive management of diabetes, particularly in the context of risk stratification for complications.

MATERIALS AND METHODS

This prospective comparative observational study was conducted at a tertiary care center over a defined study period after obtaining approval from the Institutional Ethics Committee and informed written consent from all participants. A total of 40 patients diagnosed with type 2 diabetes mellitus (T2DM) were enrolled based on predefined inclusion and exclusion criteria. The study population was divided into two equal groups of 20 patients each:

- **Group A (Uncomplicated DM):** Patients with type 2 diabetes mellitus without any clinically evident microvascular or macrovascular complications.
- **Group B (Complicated DM):** Patients with type 2 diabetes mellitus presenting with one or more established diabetic complications, including diabetic nephropathy, neuropathy, retinopathy, or cardiovascular disease.

Inclusion Criteria

1. Patients aged between 30 and 70 years diagnosed with type 2 diabetes mellitus as per ADA criteria.
2. Patients willing to provide informed consent and comply with study procedures.
3. For Group B, patients with one or more clinically and/or laboratory confirmed diabetic complications.

Exclusion Criteria

1. Patients with anemia, hemoglobinopathies, or any hematological disorders affecting iron status.
2. Patients with chronic liver disease, renal failure unrelated to diabetes, or other chronic systemic illnesses.

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3. Pregnant or lactating women.
4. Patients currently on iron supplements, vitamin B12, or folic acid therapy within the last three months.
5. History of recent acute illness, blood transfusion, or major surgery.

Clinical and Laboratory Evaluation

After recruitment, detailed demographic and clinical data including age, sex, duration of diabetes, treatment history, and presence of complications were recorded. Complications were identified through clinical examination and relevant investigations:

- **Nephropathy:** Based on elevated serum creatinine and/or microalbuminuria.
- **Retinopathy:** Confirmed by fundoscopic examination.
- **Neuropathy:** Assessed by clinical symptoms and nerve conduction studies, if indicated.
- **Cardiovascular complications:** Confirmed by ECG or echocardiographic findings.

Venous blood samples were collected from all patients after an overnight fast of at least 8 hours.

- Fasting Plasma Glucose (FPG) and Post-Prandial Glucose (PPG) were estimated using the glucose oxidase–peroxidase method.
- Serum Iron levels were measured by the colorimetric method using an automated chemistry analyzer.
- Glycated hemoglobin (HbA1c) was analyzed by High-Performance Liquid Chromatography (HPLC), which is considered the gold standard for assessing longterm glycemic control.

All biochemical analyses were performed in the hospital's central biochemistry laboratory, adhering to strict quality control protocols.

Statistical Analysis

All collected data were systematically compiled and analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 26.0 (IBM Corp., USA). Continuous variables such as age, duration of diabetes, fasting plasma glucose, post-prandial glucose, HbA1c, and

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serum iron levels were expressed as mean ± standard deviation (SD), while categorical variables including gender distribution and types of complications were summarized as frequency and percentage. The Independent Student's t-test was employed to compare the mean values of continuous variables between the two study groups, whereas the Chi-square test was applied to evaluate associations among categorical variables. The Pearson's correlation coefficient (r) was calculated to assess the strength and direction of the linear relationship between HbA1c and serum iron levels in both groups. A p-value of less than 0.05 was considered statistically significant for all analyses.

RESULT

A total of 40 patients with type 2 diabetes mellitus were included in the present study, divided equally into two groups: Group A (uncomplicated diabetes) comprising 20 patients, and Group B (complicated diabetes) comprising 20 patients with one or more diabetes-related complications such as nephropathy, retinopathy, neuropathy, or cardiovascular involvement. The demographic and clinical characteristics of both groups are summarized in Table 1.

The mean age of participants in Group A was 53.46 ± 8.22 years, while in Group B it was 56.13 ± 7.55 years, the difference being statistically non-significant ($p = 0.281$). The gender distribution was comparable across both groups (M:F ratio 11:9 in Group A and 12:8 in Group B; $p = 0.749$). However, the mean duration of diabetes was significantly longer among patients in the complicated group (9.87 ± 4.13 years) as compared to the uncomplicated group (5.74 ± 3.66 years, $p = 0.0019$*), indicating that chronicity of diabetes is strongly associated with the development of complications.

When comparing glycemic and iron parameters between the two groups (Table 2), the mean HbA1c level was significantly higher in the complicated group (9.17 ± 1.33%) than in the uncomplicated group (7.43 ± 1.20%, $p < 0.001$*). Similarly, fasting plasma glucose (FPG) and post-prandial plasma glucose (PPG) levels were markedly elevated in Group B (172.36 ± 28.92 mg/dL and 246.51 ± 42.85 mg/dL, respectively) compared with Group A (138.68 ± 22.52 mg/dL and 198.72 ± 34.65 mg/dL, $p < 0.001$* for both). These findings reflect poorer glycemic control among patients with complications.

In contrast, the mean serum iron level was significantly lower in the complicated group (62.51 ± 17.62 µg/dL) compared to the uncomplicated group (84.25 ± 14.84 µg/dL, $p < 0.001$*), suggesting an inverse relationship between iron status and disease severity. This decline in iron

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levels among complicated diabetic patients may be attributed to chronic inflammation, oxidative stress, and altered iron metabolism associated with long-standing hyperglycemia.

Correlation analysis (Table 3) revealed a negative relationship between HbA1c and serum iron levels in both groups. However, this correlation was weak and statistically non-significant in uncomplicated DM ($r = -0.21$, $p = 0.361$), whereas in the complicated DM group, it was moderate and statistically significant ($r = -0.48$, $p = 0.016$*). This indicates that as glycemic control worsens, serum iron levels tend to decrease, especially in patients with diabetes-related complications.

Among the 20 patients in the complicated DM group, the most common complication was diabetic nephropathy (40%), followed by diabetic retinopathy (30%), neuropathy (20%), and cardiovascular complications (10%) (Figure-2). These findings highlight that microvascular complications were more frequent than macrovascular ones in this cohort.

DISCUSSION

The present study demonstrates that patients with complicated type 2 diabetes mellitus (T2DM) exhibited significantly higher glycaemic indices (mean HbA1c: 9.17 ± 1.33%) and significantly lower serum iron levels (62.51 ± 17.62 µg/dL) compared to those with uncomplicated diabetes (HbA1c: 7.43 ± 1.20%; serum iron: 84.25 ± 14.84 µg/dL). A moderate inverse correlation between HbA1c and serum iron ($r = -0.48$, $p = 0.016$*) was present in the complicated-DM group, while in the uncomplicated group the correlation was weak and not statistically significant ($r = -0.21$, $p = 0.361$). These findings suggest that impaired iron status and poorer glycaemic control may co-exist in diabetic patients with complications and that iron metabolism might influence glycaemic markers in this subgroup.

The role of HbA1c as a marker of long-term glycaemic control, a predictor of diabetic complications, and even a screening/diagnostic tool for diabetes is well established. In addition, non-glycaemic factors known to affect red blood cell (RBC) turnover, haemoglobin concentration or erythrocyte lifespan may alter HbA1c independently of glucose levels [6]. One such factor is iron deficiency and anemia, which may either elevate or reduce HbA1c

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values depending on the context. As noted by Kalasker et al., alterations in RBC kinetics and haemoglobin glycation in iron-deficiency anaemia (IDA) may influence HbA1c levels [7].

Several investigations in non-diabetic and diabetic populations have specifically studied the effect of IDA on HbA1c. For example, Solomon et al. (2019) [8] reported that in diabetic patients with IDA, mean HbA₁c was significantly lower (6.18 ± 1.57%) compared to a control group (7.74 ± 1.81%; $p < 0.05$). Sinha et al. (2012) [9] and Cavagnolli et al. (2015) [10] likewise observed lower HbA1c values in participants with iron deficiency. Their explanation attributed the lower HbA1c to more severe and prolonged anemia, causing increased RBC turnover and a younger RBC population which has had less time for glycation.

Conversely, other studies have reported higher HbA1c in IDA. Ford et al. (2011) [11], Silva et al. (2015) [12], Shekhae et al. (2014) [13] and Chhabra et al. (2015) [14]observed that HbA1c levels were elevated in individuals with iron deficiency anaemia. These divergences may reflect differences in study populations, severity of anemia, glycaemic status, assay methods, and whether anaemia correction occurred.

Studies focused on RBC indices and iron parameters also present inconsistent findings. Solomon et al. (2019) [8]found that despite the lower mean HbA1c in IDA, associations between RBC count, MCV, MCH and HbA1c were not statistically significant [10]. An Indian study by Christy et al. (2014) [15] found no significant correlation between iron parameters and HbA1c ($P = 0.05$ for MCH) in diabetic patients with IDA. Similarly, Manisha et al. (2016) [16] reported comparable findings with significant differences in haemoglobin and RBC indices but inconsistent HbA1c changes.

Severity of anaemia may influence the HbA₁c relationship: Kalasker et al.[7] stratified irondeficient patients into mild (28.7%), moderate (46%), and severe (25.3%) categories. In an Indian cohort, severe anaemia was present in 76% of subjects vs 24% moderate [12]. The variable degree of anaemia complicates comparisons and may partly explain the heterogeneous HbA1c findings.

In our study, the group with complications had both higher HbA1c and lower serum iron, and the stronger negative correlation ($r = -0.48$) suggests that in the setting of long-standing diabetic complications, iron depletion might more strongly impact glycaemic control or its biochemical marker. This aligns with the concept that chronic hyperglycaemia triggers

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oxidative stress, inflammation and disturbed iron homeostasis, which may in turn reduce serum iron and alter RBC lifespan. We extend the literature by specifically examining patients with complicated vs uncomplicated diabetes.

However, the heterogeneous findings among earlier studies underscore that the effect of iron deficiency on HbA1c is complex and context-dependent. Differences in diabetic status, iron deficiency severity, type of anaemia, RBC lifespan, assay interference, and presence of complications may all modulate the relationship. Our findings support the need for careful interpretation of HbA1c in diabetic patients with iron deficiency or anaemia, and suggest that assessing iron status could add value in the management of complicated diabetics.

In summary, this study reinforces that in diabetic patients—especially those with complications—lower serum iron is associated with higher HbA1c and worse glycaemic control. Such results highlight the interplay of iron metabolism and diabetes pathophysiology and warrant consideration of iron status as part of a comprehensive diabetes evaluation. Future larger multicentric studies stratifying by anaemia severity and using standardised HbA1c assays will help elucidate the mechanistic links.

CONCLUSION

The present study demonstrates a significant association between poor glycemic control and reduced serum iron levels among patients with type 2 diabetes mellitus. Patients with diabetic complications exhibited markedly higher HbA1c levels and lower serum iron concentrations compared to those without complications, indicating that worsening glycemic status may adversely affect iron metabolism. A moderate inverse correlation between HbA1c and serum iron in the complicated group further supports this relationship. These findings suggest that monitoring iron status alongside glycemic indices can provide valuable insight into the metabolic and inflammatory changes associated with chronic diabetes. Early detection and correction of altered iron parameters may help prevent or delay the progression of diabetic complications, underscoring the importance of a comprehensive biochemical evaluation in the routine management of diabetes mellitus.

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TABLES AND FIGURES

Table 1. Demographic Profile of Study Participants (n = 40)

Parameter	Group A (Uncomplicated DM) [n=20]	Group B (Complicated DM) [n=20]	*p*-value
Mean Age (years)	53.46 ± 8.22	56.13 ± 7.55	0.291
Gender (M:F)	11 : 9	12 : 8	0.749

Table 2. Comparison of Glycemic and Iron Parameters between Groups

Parameter	Group A (Uncomplicated DM) [n=20]	Group B (Complicated DM) [n=20]	*p*-value
HbA1c (%)	7.43 ± 1.20	9.17 ± 1.33	**< 0.001***

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Serum Iron (µg/dL)	84.25 ± 14.84	62.51 ± 17.62	**< 0.001***
Fasting Plasma Glucose (mg/dL)	138.68 ± 22.52	172.36 ± 28.92	**< 0.001***
Post-Prandial Glucose (mg/dL)	198.72 ± 34.65	246.51 ± 42.85	**< 0.001***

Table 3. Correlation Between HbA1c and Serum Iron Levels

Parameter	Group	Pearson's *r*	*p*-value
HbA1c vs Serum Iron	Uncomplicated DM (n=20)	−0.21	0.361
	Complicated DM (n=20)	**−0.48**	**0.016***

Figure 1. Mean duration of Diabetes in both groups

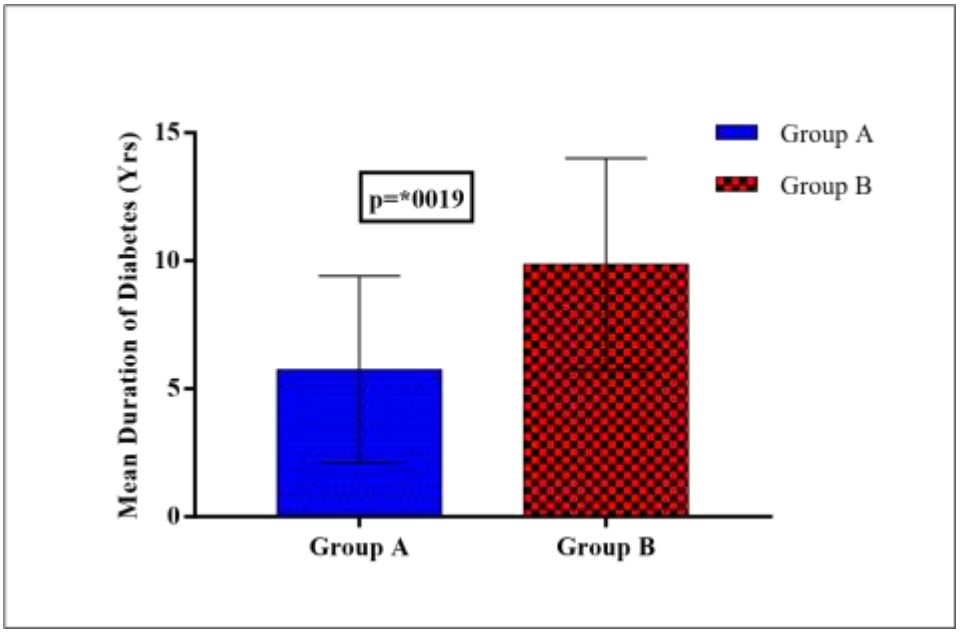

Figure 2. Frequency of Complications in Group B

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