

Ferritin Levels in Poorly Controlled Type II Diabetics Versus Patients with Optimal Control

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a growing global health concern characterized by chronic hyperglycemia, insulin resistance and associated complications. Serum ferritin an iron storage protein and inflammatory marker has been linked to poor glycemic control and may provide insight into the interplay between iron metabolism, inflammation and diabetes management.

Objective: To assess the correlation of glycemic control with serum ferritin levels.

Methods: This comparative cross-sectional study was performed at the Department of Pathology and Endocrinology, Fauji Foundation Hospital, Rawalpindi from December 2023 to May 2024. Data of patients attending the diabetic clinic were included and distributed into two groups: Group A (patients with good glycemic control) and Group B (patients with poor glycemic control). Blood samples from patients included in this study were collected and analyzed for the levels of serum ferritin, CRP and HbA1C. Descriptive variables were presented as frequency, percentages and median accordingly.

Results: In this study of 160 participants, divided based on glycemic control, group A had a lower median HbA1C of 5.70% compared to 8.10% in group B. Group B also had a higher median serum ferritin level (348.00 µg/L versus 161.5 µg/L). Additionally, group A had lower levels of C-reactive protein (0.3 mg/dL) compared to group B (0.4 mg/dL). Higher serum ferritin and CRP levels were strongly correlated to increased HbA1C levels.

Conclusion: Increased ferritin and CRP levels are strongly related to poorly controlled T2DM. Monitoring ferritin levels in glycemic care can enhance patient outcomes by allowing for better risk assessment and targeted interventions. Future research in various regions must be done to develop effective therapies that utilize ferritin monitoring in managing T2DM globally.

Key words: HbA1C, serum ferritin, CRP, glycemic control, T2DM.

Introduction

Type II diabetes mellitus (T2DM) is one of the greatest health challenges worldwide, with roughly 537 million adults affected around the world as of 2021, a number that threatens to rise to 783 million by 2045, as mentioned in International Diabetes Federation (IDF) Diabetes Atlas, 2021. In

a recent study in Pakistan, prevalence of 30.8% has been reported among those who are 20 to 79 years old.¹ Hence, strategic interventions against metabolic disorders and the accompanying complications are necessary to address this global crisis. T2DM, along with elevated blood sugar levels, is fundamentally linked to inflammation and oxidative stress, which play crucial roles in insulin resistance and organ damage.²

Serum ferritin, a vital protein responsible for iron storage in the body, is not only an indicator of iron levels but also studied as a marker of inflammation.³ Elevated ferritin levels are strongly associated with insulin resistance, β -cell dysfunction, and poor blood sugar control, establishing a clear connection between iron metabolism and diabetes.⁴ Iron imbalances often occur in T2DM as a result of persistent inflammation, oxidative stress, or genetic factors.⁵ Moreover, elevated ferritin levels are commonly found in individuals with metabolic syndrome, which

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Authors Contribution

SK & AN conceptualized the project. SK & AMG did the data collection. SK & SA performed the statistical analysis. SK & HA did the literature search. Drafting, revision & writing of manuscript were done by SK & EN.

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is directly correlated with insulin resistance and fatty liver disease.⁶ A comprehensive meta-analysis established that higher ferritin level is an independent risk factor with 23% increased risk for developing T2DM.⁷

In a study regarding the role of CRP and glycemic control, it was shown that the CRP levels remained significantly higher in patients diagnosed with T2DM, either obese or overweight.⁸ Inflammation, a hallmark of poorly controlled T2DM, significantly increases iron storage in specific cells, leading to higher ferritin levels in the bloodstream.⁹ However, despite a positive correlation shown in a study, of HbA1C with serum ferritin and CRP ($p=0.911$ and $p=0.865$ respectively), no significant link has been found between ferritin levels and the onset of diabetes after adjusting for inflammation markers like CRP, highlighting the complexity of this issue.¹⁰

Serum ferritin has been associated with poor glycemic control in T2DM, yet it is not straightforward because it is also an inflammatory marker. The research aims to compare ferritin concentrations in poorly and optimally controlled T2DM patients with CRP and demographics in order to determine whether high ferritin indicates hyperglycemia specifically or underlying inflammation.

Methods

This comparative Cross Sectional study was conducted at the Department of Pathology and Endocrinology, Fauji Foundation Hospital, Rawalpindi from December 2023 to May 2024, after the approval of Institutional Review Board. A sample size of 160 patients (80 in each group) was statistically calculated by taking mean ferritin levels as 73.3 ± 56.6 ng/ml among people with controlled glycemic group and 269.8 ± 347.1 ng/ml amongst uncontrolled glycemic group.¹¹

All patients irrespective of gender, diagnosed with type 2 diabetes mellitus, with no previous complications were included in this study. Patients with any disease or medical condition causing high CRP and Ferritin levels, patients with prior iron supplements, blood transfusions and diabetic complications like neuropathy, retinopathy and nephropathy were excluded from this study.

After obtaining informed written consent, data were collected from patients presenting to the diabetic clinic of the Internal Medicine Outpatient Department of the hospital. The patients were enrolled and categorized based on glycemic control using HbA1c levels. Patients with HbA1c $\leq 7.5\%$ were classified as having optimally controlled

diabetes mellitus (Group A) while those with HbA1c $> 7.5\%$ were classified as having poorly controlled diabetes mellitus (Group B) in accordance with NICE guidelines. A venous blood sample of 4–5 mL was collected from each participant. Samples for HbA1c estimation were collected in EDTA tubes and analyzed using the CH Atellica system by the photometric method. Samples for serum ferritin and CRP were collected in plain red-top tubes. Serum ferritin levels, measured in $\mu\text{g/L}$, were categorized according to NICE guidelines as low ($<15 \mu\text{g/L}$), borderline ($16-40 \mu\text{g/L}$), normal ($41-400 \mu\text{g/L}$) and high ($>400 \mu\text{g/L}$). Serum ferritin analysis was performed using the IM Atellica system by enzyme immunosorbent assay. CRP levels were used as a screening marker for inflammation and were analyzed quantitatively using the Atellica system. CRP values ≤ 0.3 mg/dL were considered optimal, values between $0.3-1.0$ mg/dL mildly elevated, $1-10$ mg/dL moderately elevated and levels >10 mg/dL highly elevated as per NICE guidelines.

Data analysis was completed using SPSS 22.0. Shapiro-Wilk test, which was used to analyze the normality of the data. Frequency and percentage was used to represent qualitative data. Chi square test (for qualitative variables) and Mann-Whitney U-test (for non-normal data) were applied and p-value of ≤ 0.05 was considered as statistically significant.

Results

In this study, 160 study subjects were enrolled and divided into two equal groups according to glycemic control status. 76 participants (47.5%) were males and 84 were (52.5%) females. Median age was 50 (54-45) years. The detail of age and gender of participants is shown in Table-1. The Median of HbA1C was low in group A 5.70 (6.30-4.23)% versus group B of patients 8.10 (8.60-7.90)%. However, Median of serum Ferritin level was high in patients of group B [348.00 (407.50-219.75)] as compared to group A [161.5 (243.00 – 99.25)] i.e. p value <0.01 . Furthermore, group A patients had less CRP [0.3 (0.6-0.2) (mg/dL)] as compared to Group B [0.4 (2.60-0.29) (mg/dL)] as p value =0.007 shown in Table-2. We observed that, as serum ferritin level ($\mu\text{g/L}$) was increased then HbA1C (%) was also increased.

A correlation between inflammatory markers and glycemic control is shown in Table-3. Serum ferritin showed a moderate positive correlation with HbA1c ($r = 0.491$, $p <0.001$) indicating that higher ferritin levels were associated with poorer glycemic control. Similarly, C-reactive protein (CRP) showed a weak but significant positive correlation with

Table 1: Demographic characteristics of the study participants. (n=160)

Variables	Categories	Study Groups		Total (n=160) n (%)	p-value
		Group A (n=80) n (%)	Group B (n=80) n (%)		
Gender	Male	44 (57.9)	32 (42.1)	76 (47.5%)	0.081
	Female	36 (42.9)	48 (57.1)	84 (52.5%)	
Age Groups	18-33	11 (73.3)	4 (26.7)	15 (9.4%)	0.145
	34-49	28 (45.2)	34 (54.8)	62 (38.8%)	
	50-65	41 (49.4)	42 (50.6)	83 (51.9%)	

Table-2: Comparison of HbA1C, ferritin and CRP in both groups (n=160)

Parameters	Group A (n=80) Median (IQR)	Group B (n=80) Median (IQR)	p-value
HbA1C (%)	5.70 (6.30 – 4.23)	8.10 (8.60 – 7.90)	< 0.001
Ferritin level (ug/L)	161.5 (243.00 – 99.25)	348.00 (407.50 – 219.75)	<0.001
CRP (mg/dL)	0.3 (0.6 -0.2)	0.4 (2.60 – 0.29)	0.007

HbA1c ($r = 0.252$, $p = 0.001$) suggesting that increasing systemic inflammation is also linked with elevated HbA1c levels.

Table 3: Correlation analysis of serum ferritin and CRP with HbA1c.

	HbA1c	
	r	p-Value
Ferritin	0.491	<0.001
CRP	0.252	0.001

Discussion

Present study reveals a notable correlation between poor glycemic control and increased serum ferritin concentrations in patients who are diagnosed with type 2 diabetes mellitus (T2DM). Participants exhibiting uncontrolled glucose levels (Group B: median HbA1c 8.10%) demonstrated markedly elevated ferritin values (348 µg/L) relative to their counterparts with stabilized glycemic profiles (Group A: 161.5 µg/L, $p < 0.001$).

Recent emerging data also suggests that iron homeostasis is a key metabolic marker of prolonged hyperglycemia. A cross-sectional study of 180 patients in Hyderabad, Pakistan demonstrated that patients with hyperglycemia had higher serum ferritin levels than those having good glycemic control (56.0% and 44.0% respectively) emphasizing ferritin accumulation as a sequela of glucose dysregulation¹². Parallel findings from a study in Bangladesh found that the mean serum ferritin level was significantly elevated in the group with poor glycemic control compared to the group with good glycemic control ($p < 0.05$). However,

there were no statistically significant differences in terms of age, sex, BMI, or duration of diabetes between the two groups ($p > 0.05$), further substantiating the bidirectional interplay between glucose metabolism and iron retention.¹³

Other research conducted in the region of South Asia has also supported results of this study. A study conducted in a tertiary care hospital of India has shown that diabetic patients with normal glycemic blood levels had a mean serum ferritin level of 119.07 ± 58.99 ng/ml, which was lower than those with poor glycemic control, who had a mean level of 331.11 ± 140.69 ng/ml.¹⁴ Another study concluded that serum ferritin may play an important role in monitoring of diabetic control in patients.¹⁵ These findings necessitate the need for more biochemical evidence to support the gathered data. This study focused on a relatively higher ratio of females (52.5%). In a study in China, it was observed that higher ferritin levels in the bloodstream were linked to increased incidence of type 2 diabetes (T2DM), with the association being stronger in women than in men.¹⁶ Contrastingly, another study showed the hazard ratios for developing diabetes associated with increased serum ferritin levels were as follows: 1.17 (95% Confidence Interval [CI] 1.03 to 1.34) for the total population, 1.20 (95% CI 1.00 to 1.43) for men, and 1.03 (95% CI 0.82 to 1.31) for women, indicating no role of gender distribution and negating any age dependent inflammatory reaction and diminished efficiency of iron clearance.¹⁷

CRP is typically elevated in individuals with increased blood sugar, supporting the connection between ferritin and diabetes.¹⁸ Increase in C-reactive protein levels in Group B patients (median

CRP: 0.4 mg/dL vs. 0.3 mg/dL, $p = 0.007$) shows its importance in monitoring of patients with T2DM. Increased glycemic levels can increase the production of IL-6, leading to synthesis of hepcidin and reducing the activity of Ferroprotein. This leads to excess iron storage within the cell.¹⁹ Another research conducted in Pakistan further validated these dynamics, demonstrating that CRP concentrations showing a positive correlation with higher levels of HbA1C.²⁰ Collectively, these observations imply that oxidative stress and inflammatory processes are significant contributors to the variations in ferritin levels in individuals with diabetes.

This study limits causal interpretations of other influencers of serum ferritin levels such as dietary iron, genetic polymorphisms like HFE gene mutations etc. Its population was also limited to one clinical setting, resulting in a lack of diversity of patients.

Conclusion

Increased ferritin and CRP levels have shown to be strongly correlated to poor control of blood glucose levels in diverse populations. This indicates a connection between inflammation and ferritin dysregulation with poor diabetic control.

Incorporating ferritin monitoring into diabetic care can prove to be beneficial to patient care. It can help us better assess risks and create targeted interventions that truly improve patient outcomes. By paying closer attention to ferritin levels, we can modify our approach and ensure that patients receive the support they need to manage their health effectively. Future research in different demographic populations must be done in order to prioritize the development and implementation of targeted therapies by monitoring ferritin levels in diverse ethnic groups to confirm and establish the global effectiveness in management of T2DM.

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Availability of Data: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval: The Ethical Review Committee of Fauji Foundation Hospital, Rawalpindi approved the study via letter no. 619/RC/FFH/RWP dated 02/12/2023.

Conflict of Interest: None declared.

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