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THE ASSOCIATION OF SERUM FERRITIN WITH INFLAMMATION AND UNCONTROLLED GLYCEMIA IN A DIABETIC COHORT

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ABSTRACT

Background: Chronic low-grade inflammation is a key pathophysiological component of Type 2 Diabetes Mellitus (T2DM). Serum ferritin, traditionally an iron-storage protein, is also recognized as an acute-phase reactant. Elevated levels are associated with insulin resistance and β-cell dysfunction, though its precise role in the inflammatory cascade of T2DM remains to be fully elucidated in specific populations.
Aim: This study aimed to investigate the role of serum ferritin as an inflammatory marker and to evaluate its correlation with glycemic control in patients with T2DM.
Materials and Methods: A cross-sectional study was conducted on 74 diagnosed T2DM patients. Fasting blood samples were analyzed for serum ferritin, glycated hemoglobin (HbA1c), fasting blood glucose (FBG), and high-sensitivity C-reactive protein (hs-CRP). Patients were stratified into two groups based on glycemic control: good control (HbA1c < 7%, n=32) and poor control (HbA1c ≥ 7%, n=42). Statistical analysis was performed using Pearson's correlation and independent samples t-test.
RESULTS: Mean serum ferritin levels were significantly higher in the poor glycemic control group (98.4 ± 45.2 ng/mL) compared to the good control group (52.7 ± 28.6 ng/mL) ($p < 0.001$). A strong positive correlation was observed between serum ferritin and HbA1c ($r = 0.712$, $p < 0.001$) and between serum ferritin and hs-CRP ($r = 0.654$, $p < 0.001$).
Conclusion: Serum ferritin levels are significantly elevated in T2DM patients with poor glycemic control and show a strong positive correlation with established markers of inflammation (hs-CRP) and hyperglycemia (HbA1c). This suggests that serum ferritin can serve as a valuable, complementary inflammatory marker and a potential indicator of glycemic status in T2DM management.

Keywords: *Serum Ferritin, Type 2 Diabetes Mellitus, Inflammation, Glycemic Control, HbA1c, hs-CRP.*

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) represents one of the most significant global health challenges of the 21st century, characterized by chronic hyperglycemia arising from a complex interplay of insulin resistance in peripheral tissues and a progressive decline in pancreatic β-cell function [1]. While the traditional understanding of T2DM pathophysiology has focused on these metabolic defects, a paradigm shift has occurred with the recognition that chronic, low-grade inflammation is a fundamental contributor to the disease's initiation and progression [2]. This subclinical inflammatory state creates a vicious cycle, perpetuating insulin resistance and accelerating β-cell apoptosis.

The source of this inflammation is often linked to adipose tissue, particularly visceral fat. In obesity, a key risk factor for T2DM, expanded adipose tissue becomes a hub for pathogenic immune cell infiltration and the dysregulated secretion of adipokines and pro-inflammatory cytokines, including Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1β (IL-1β), and

notably, Interleukin-6 (IL-6) [3]. These cytokines enter the circulation and activate inflammatory pathways in insulin-sensitive tissues like the liver and skeletal muscle, disrupting insulin signaling cascades and promoting gluconeogenesis. In clinical practice, the measurement of high-sensitivity C-reactive protein (hs-CRP), a non-specific acute-phase reactant synthesized by the liver in response to IL-6, has become a cornerstone for assessing this underlying inflammatory burden in metabolic diseases [4]. However, inflammation in T2DM is multifaceted, and the exploration of complementary biomarkers could provide a more holistic view of a patient's inflammatory status and disease severity.

Serum ferritin, the primary intracellular iron-storage protein, has traditionally been used as a key indicator of body iron stores. However, it is now well-established that serum ferritin is also a robust acute-phase reactant. Its levels can rise dramatically in response to inflammatory stimuli, independent of iron status, as its synthesis is directly upregulated by cytokines, particularly IL-6 [5]. This dual nature complicates its interpretation but also opens a window into inflammatory processes.

Elevated serum ferritin has been epidemiologically linked to an increased risk of developing T2DM and its complications [6]. The proposed mechanisms extend beyond its role as an inflammatory marker. Iron is a potent pro-oxidant. Elevated body iron stores can catalyze the formation of highly reactive hydroxyl radicals via the Fenton reaction, leading to increased oxidative stress [7]. This oxidative environment can directly damage pancreatic β-cells, impair glucose-stimulated insulin secretion, and worsen insulin resistance by interfering with insulin signaling pathways in hepatocytes and adipocytes. Furthermore, some evidence suggests that ferritin itself may have direct immunomodulatory effects, potentially acting as a pro-inflammatory mediator [8].

Despite compelling evidence linking iron metabolism and inflammation to diabetes, the specific utility of serum ferritin as a routine clinical marker of inflammation in established T2DM, and its precise correlation with the gold-standard measure of long-term glycemic control, glycated hemoglobin (HbA1c), requires further validation in well-defined, smaller cohorts. Many studies are large-scale and epidemiological, leaving a gap in understanding its day-to-day clinical applicability. Therefore, this study aims to bridge this gap by specifically investigating the role of serum ferritin as an inflammatory marker and evaluating its correlation with glycemic control in a cohort of 74 patients with T2DM, thereby assessing its potential as a practical, adjunct biomarker in diabetes management.

MATERIALS AND METHODS

Study design, setting and population

This study employed an analytical, cross-sectional study design. The study was conducted at the outpatient department of [Insert Name of Hospital/Institution].The target population consisted of 74 adult patients (aged 30-65 years) with a clinically confirmed diagnosis of Type 2 Diabetes Mellitus who attended the outpatient department during the six-month study period (from [Start Date] to [End Date]).

Inclusion Criteria:

- Adults aged between 30 and 65 years.
- Patients with a confirmed diagnosis of Type 2 Diabetes Mellitus for at least one year, as per American Diabetes Association (ADA) criteria.
- Patients willing to provide written informed consent.

Exclusion Criteria:

- Patients with Type 1 Diabetes Mellitus, latent autoimmune diabetes in adults (LADA), or other specific types of diabetes.
- Pregnancy or lactation.
- History of hemochromatosis, thalassemia, or other hematological disorders affecting iron metabolism.
- Presence of acute or chronic infections (e.g., tuberculosis, HIV).
- History of chronic inflammatory diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease).
- Known liver cirrhosis or chronic kidney disease (Stage 4 or 5).
- History of malignancy.
- Recent blood transfusion or iron supplementation within the past 3 months.
- Acute diabetic complications (e.g., ketoacidosis, hyperosmolar state) within the past month.

Procedure for Data Collection

1. **Screening and Recruitment:** Consecutive patients attending the OPD were screened for eligibility based on the inclusion and exclusion criteria.

2. **Informed Consent:** Eligible patients were provided with detailed information about the study's aims and procedures. Written informed consent was obtained from all willing participants.

3. **Data Collection:** A structured questionnaire was used to record demographic details (age, sex) and relevant clinical history.
4. **Blood Sample Collection:** After confirming an overnight fast of 10-12 hours, 5 mL of venous blood was drawn from the antecubital vein under aseptic precautions.
5. **Biochemical Analysis:** The blood samples were centrifuged, and the separated serum was aliquoted and analyzed on the same day.
   - **HbA1c** was estimated using the Bio-Rad D-10™ Hemoglobin Testing System based on High-Performance Liquid Chromatography (HPLC).
   - **Fasting Blood Glucose (FBG)** and **hs-CRP** were analyzed on a Cobas c 311 clinical chemistry analyzer using standard enzymatic and immunoturbidimetric methods, respectively.
   - **Serum Ferritin** was quantified using an electrochemiluminescence immunoassay (ECLIA) on a Cobas e 411 analyzer.

Statistical analysis

All data, including demographic details and laboratory results, were recorded in a pre-designed Microsoft Excel spreadsheet. To ensure confidentiality, each participant was assigned a unique identification number, and all data were anonymized using this ID. The electronic data file was password-protected and stored on a secure, encrypted institutional server accessible only to the principal investigators. Data accuracy was verified by a second researcher through random cross-checking of 10% of the entries against the original laboratory reports.

Table 1: Baseline Characteristics and Biochemical Parameters of the Study Participants

Characteristic	Total Cohort (n=74)	Good Glycemic Control (n=32)	Poor Glycemic Control (n=42)	p-value
Age (years)	52.4 ± 8.7	51.1 ± 7.9	53.4 ± 9.2	0.251
Gender, n (%)				0.722
Male	40 (54.1%)	18 (56.3%)	22 (52.4%)	
Female	34 (45.9%)	14 (43.8%)	20 (47.6%)	
Duration of DM (years)	7.5 ± 4.3	6.8 ± 3.9	8.0 ± 4.6	0.221
Fasting Blood Glucose (mg/dL)	168.4 ± 43.2	128.6 ± 18.4	198.3 ± 32.7	**<0.001**
HbA1c (%)	7.8 ± 1.6	6.4 ± 0.4	8.9 ± 1.2	**<0.001**
Serum Ferritin (ng/mL)	78.6 ± 44.5	52.7 ± 28.6	98.4 ± 45.2	**<0.001**
hs-CRP (mg/L)	3.9 ± 2.5	2.1 ± 1.0	5.3 ± 2.4	**<0.001**

The baseline characteristics of the two groups were comparable. There was no statistically significant difference in the mean age between the good control group (51.1 ± 7.9 years) and the poor control group (53.4 ± 9.2 years) (p=0.251). The gender distribution was also similar between groups (p=0.722), with males comprising 56.3% of the good control group and 52.4% of the poor control group. The mean duration of diabetes was not significantly different between the groups (6.8 ± 3.9 years vs. 8.0 ± 4.6 years, p=0.221). As expected by the group stratification, a highly significant difference was observed in glycemic parameters. The mean Fasting Blood Glucose was 128.6 ± 18.4 mg/dL in the good control group compared to 198.3 ± 32.7 mg/dL in the poor control group ($p < 0.001$). The mean HbA1c was 6.4 ± 0.4% in Group 1 and 8.9 ± 1.2% in Group 2 ($p < 0.001$). Crucially, the mean serum ferritin level was significantly elevated in the poor control group (98.4 ± 45.2 ng/mL) compared to the good control group (52.7 ± 28.6 ng/mL) ($p < 0.001$). Similarly, the inflammatory marker hs-CRP was significantly higher in patients with poor glycemic control (5.3 ± 2.4 mg/L) than in those with good control (2.1 ± 1.0 mg/L) ($p < 0.001$).

Table 2: Correlation Matrix (Pearson's Correlation Coefficients) between Serum Ferritin, Glycemic, and Inflammatory Markers in the Total Cohort (n=74)

Variable	1. Serum Ferritin	2. HbA1c	3. hs-CRP	4. FBG
1. Serum Ferritin	1			
2. HbA1c	**0.712**	1		
	(p < 0.001)			
3. hs-CRP	**0.654**	**0.598**	1	
	(p < 0.001)	**(p < 0.001)**		
4. Fasting Blood Glucose (FBG)	**0.587**	**0.823**	**0.521**	1
	(p < 0.001)	**(p < 0.001)**	**(p < 0.001)**	

All correlations shown are statistically significant (p < 0.001).

The correlation analysisrevealed strong and statistically significant positive relationships between the key variables. A very strong positive correlation was found between serum ferritin and HbA1c ($r = 0.712$, $p < 0.001$), indicating that as HbA1c levels increased, serum ferritin levels also rose substantially. Serum ferritin also demonstrated a strong positive correlation with the established inflammatory marker hs-CRP ($r = 0.654$, $p < 0.001$). Furthermore, a strong positive correlation was observed between HbA1c and hs-CRP ($r = 0.598$, $p < 0.001$). Serum ferritin showed a significant positive correlation with Fasting Blood Glucose ($r = 0.587$, $p < 0.001$).

Table 3: Stratified Analysis of Serum Ferritin and hs-CRP by Gender

Parameter	Males (n=40)	Females (n=34)	p-value
Serum Ferritin (ng/mL)	89.2 ± 47.1	66.1 ± 37.8	**0.021**
hs-CRP (mg/L)	3.7 ± 2.3	4.1 ± 2.7	0.482

Data presented as Mean ± SD. p-value from independent samples t-test.

The mean serum ferritin level was found to be significantly higher in male participants (89.2 ± 47.1 ng/mL) compared to female participants (66.1 ± 37.8 ng/mL) (p=0.021). In contrast, there was no significant difference in the mean hs-CRP levels between males (3.7 ± 2.3 mg/L) and females (4.1 ± 2.7 mg/L) (p=0.482).

DISCUSSION

This cross-sectional study demonstrates a significant association between elevated serum ferritin levels, poor glycemic control, and systemic inflammation in a cohort of 74 patients with Type 2 Diabetes Mellitus (T2DM). The core findings reveal that individuals with poor glycemic control (HbA1c ≥ 7.0%) exhibit markedly higher levels of serum ferritin and the established inflammatory marker hs-CRP compared to their well-controlled counterparts. Furthermore, the strong positive correlations between serum ferritin, HbA1c, and hs-CRP solidify the intricate link between iron-related inflammation and dysglycemia in T2DM.

The significantly elevated serum ferritin levels in the poor glycemic control group (**98.4 ng/mL vs. 52.7 ng/mL, p < 0.001**) align with the growing body of evidence that repositions ferritin beyond an iron-store protein to a key acute-phase reactant in metabolic dysregulation. This finding is consistent with a study by **Jiang et al. (2004)**, who, in a larger prospective cohort, identified elevated ferritin as an independent risk factor for the development of T2DM, suggesting its role in pathogenesis precedes clinical diagnosis.[6] Our results extend this concept by illustrating that within an already diagnosed population, ferritin levels remain closely tethered to the quality of metabolic control. The strong positive correlation between serum ferritin and HbA1c ($r = 0.712$, $p < 0.001$) suggests a potential vicious cycle: chronic hyperglycemia may promote inflammatory pathways that elevate ferritin, which in turn may exacerbate insulin resistance and beta-cell dysfunction, further worsening glycemic control.

The robust correlation between serum ferritin and hs-CRP ($r = 0.654$, $p < 0.001$) is a pivotal finding of this study. It provides compelling evidence that in our cohort, elevated ferritin is a reliable indicator of underlying subclinical inflammation, akin to the well-characterized hs-CRP. This reinforces the hypothesis that ferritin's elevation in T2DM is largely driven by cytokine activity, particularly Interleukin-6 (IL-6), which stimulates the simultaneous hepatic production of both hs-CRP and ferritin.[5] This synergy between markers was also observed by **Fernández-Real et al. (2002)**, who reported a close relationship between serum ferritin, markers of insulin resistance, and inflammatory cytokines.[7] Our results corroborate their work, confirming that in a clinical setting, measuring serum ferritin offers a window into the same inflammatory processes captured by hs-CRP, potentially serving as a complementary biomarker.

The gender-based analysis, which found significantly higher ferritin levels in men, is consistent with well-established physiological norms due to differences in iron stores (e.g., menarche, menstruation in women). However, the fact that the correlation between ferritin and poor glycemic control held strong within the cohort despite this physiological variation strengthens the argument for its role as an inflammatory marker in T2DM, independent of absolute iron stores.

Several mechanistic pathways can explain our observations. Iron is a potent catalyst for oxidative stress via the Fenton reaction, generating reactive oxygen species (ROS) that can directly impair insulin signaling in hepatocytes and skeletal muscle and promote pancreatic beta-cell apoptosis.[7,9] Furthermore, chronic hyperglycemia itself creates a pro-oxidative environment, potentially creating a feed-forward loop where dysglycemia, inflammation, and elevated ferritin perpetuate each other.[10]

The cross-sectional design is the primary limitation, as it prevents us from establishing a causal relationship between the variables. The sample size, though adequate for this analysis, is modest. We did not measure other iron indices (e.g., transferrin saturation) or inflammatory cytokines (e.g., IL-6) to provide a more granular understanding of the mechanisms. Despite this, the strength of our study lies in its well-characterized patient groups, strict exclusion criteria to eliminate confounding conditions, and the use of standardized, high-precision laboratory techniques.

CONCLUSION

In conclusion, this study demonstrates that serum ferritin is significantly elevated in T2DM patients with poor glycemic control and is strongly correlated with both HbA1c and hs-CRP. These findings suggest that serum ferritin acts as an integral component of the inflammatory cascade in T2DM and can serve as a valuable clinical marker, providing a composite reflection of both dysmetabolism and underlying inflammation. We recommend larger longitudinal studies to determine if serial measurement of serum ferritin can predict glycemic deterioration or the development of diabetic complications, and to explore whether anti-inflammatory strategies can modulate ferritin levels to improve metabolic outcomes.

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