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Serum Ferritin as a Predictive Biomarker for Glycemic Control in Type 2 Diabetes; A Cross-sectional Analysis

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Author`s Contribution

[1,2]Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work,[3-5,6]Drafting the work or revising it critically for important intellectual content

Funding Source: None
Conflict of Interest: None

Received: June 29, 2024
Accepted: Nov 12, 2024

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ABSTRACT

Objective to determine whether serum ferritin is associated with glycemic control, measured by HbA1c, in Pakistani adults with T2DM.

Methodology: A descriptive cross-sectional study was conducted at Nishtar Medical University/Hospital, Multan, from 24 August 2022 to 24 February 2023. Consecutive adults aged 30–70 years with physician-diagnosed T2DM of >2 years' duration were enrolled (n = 151). Patients on iron therapy, with anemia, acute infection, blood donation, pregnancy, or chronic renal/hepatic disease were excluded. Serum ferritin (chemiluminescent immunoassay) and HbA1c (HPLC) were measured. Elevated ferritin was defined as >250 ng/mL in males or >120 ng/mL in females. Correlations were assessed with Spearman's ρ; chi-square tests were used post-stratification. Significance was set at $p \leq 0.05$.

Results: Mean age was 48.8 ± 10.8 years; 57.0 % were female. Median HbA1c was 7.7 % (IQR 3.3); 58.9 % (n = 89) had uncontrolled diabetes (HbA1c ≥ 7 %). Median ferritin was 96 ng/mL (IQR 131), with elevated levels in 30.5 % of participants. HbA1c correlated positively with ferritin (ρ = 0.252, p = 0.002). Elevated ferritin was more common in uncontrolled versus controlled diabetes (44.9 % vs 9.7 %; $p < 0.001$). The HbA1c-ferritin correlation remained significant among females, obese patients, rural residents, non-hypertensive individuals, and those without a family history of hypertension.

Conclusions: Serum ferritin is independently associated with poorer glycemic control in Pakistani adults with T2DM and may serve as a practical adjunct biomarker for risk stratification in routine care. Prospective studies are needed to validate its predictive value and explore therapeutic strategies targeting iron overload.

Keywords: Serum ferritin, Type 2 diabetes mellitus, Glycemic control, Biomarker

Cite this article as: Fatima F, Zainab M, Zainab A, Khalid MU, Rehman ZU, Amjad MB. Serum Ferritin as a Predictive Biomarker for Glycemic Control in Type 2 Diabetes; A Cross-sectional Analysis. Ann Pak Inst Med Sci. 2024; 20(4):850-854. doi. 10.48036/apims.v20i4.1120.

Introduction

Type 2 diabetes mellitus (T2DM) represents a pervasive global health crisis, characterized by chronic hyperglycemia due to insulin resistance and β-cell dysfunction. The International Diabetes Federation estimates that approximately 537 million adults worldwide live with diabetes, a figure projected to rise to 783 million by 2045, with T2DM constituting over 90% of cases.[1] Inadequate glycemic control accelerates microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (cardiovascular disease) complications,[2] underscoring the imperative for biomarkers that complement HbA1c – the current gold standard for monitoring long-term glycemic status.[3]

Iron metabolism dysregulation has emerged as a critical factor in T2DM pathogenesis. Serum ferritin, an iron-storage protein and acute-phase reactant, reflects body iron stores and exhibits strong associations with insulin resistance.[4] Mechanistically, elevated iron promotes oxidative stress, damaging pancreatic β-cells and impairing insulin secretion [5], while hepatic iron overload reduces insulin clearance and enhances gluconeogenesis.[6] Meta-analyses confirm that high serum ferritin increases T2DM risk by 62% (pooled RR: 1.62; 95% CI: 1.35–1.94) [7], and longitudinal studies demonstrate its predictive capacity for incident diabetes.[8]

Despite robust evidence, significant gaps persist. Most data derive from Western or East Asian populations [8,9], with limited representation from South Asia – a region

experiencing exponential T2DM growth due to genetic susceptibility and lifestyle transitions.[10] Pakistan's T2DM prevalence (17.1%) exemplifies this burden[11] yet ferritin's role in glycemic control remains underexplored in this population. Additionally, confounding factors like subclinical inflammation[12], renal impairment, and hematologic disorders are frequently unaddressed in existing literature.

Preliminary evidence from a Pakistani cohort by Memon *et al.* [13] reported elevated ferritin (≥307 µg/L) in 60.5% of T2DM patients, with significantly higher levels in those with poor glycemic control (HbA1c ≥7%; p=0.044). Building on this, we investigate serum ferritin as a predictive biomarker for glycemic control in T2DM, adjusting for key confounders. Our findings may advocate for integrating ferritin assessment into routine diabetes management protocols to enable early intervention.

Methodology

Following approval from the institutional ethics committee, this descriptive cross-sectional study was conducted at Nishtar Medical University/Hospital, Multan, in collaboration with the Department of General Medicine and Department of Pathology. The study spanned six months from August 24, 2022, to February 24, 2023. A total of 151 patients with type 2 diabetes mellitus (T2DM) meeting inclusion criteria were enrolled using non-probability consecutive sampling. The sample size was calculated by using WHO sample size calculator with help of 95% confidence level, p = 26% (anticipated frequency of elevated serum ferritin in diabetes), and d = 7% (margin of error). All participants provided written informed consent after being informed of study objectives, assured confidentiality, and advised of minimal risks.

Inclusion criteria comprised adults aged 30–70 years of both genders with physician-diagnosed T2DM for >2 years, confirmed by ongoing anti-diabetic medication. Exclusion criteria included: iron supplementation therapy, anemia (hemoglobin <11.5 g/dL for females or <13 g/dL for males), recent infections (<4 weeks), blood donations within three months, comorbidities (coronary artery disease, acute infections, stroke, thyrotoxicosis, hemochromatosis, chronic renal/liver disease), pregnancy, or declined consent. Demographic and clinical variables—age, gender, residential status (urban/rural), diabetes duration, obesity status, family history of diabetes, and hypertension—were documented using structured proformas. Diabetes control was classified as controlled (HbA1c <7%) or uncontrolled (HbA1c ≥7%). Obesity was defined as BMI >27.5 kg/m² (weight[kg]/height[m]²), and hypertension as antihypertensive medication use for >2 years. Elevated serum ferritin was gender-stratified: >250 ng/mL (males) or >120 ng/mL (females).

A 3 mL venous blood sample was collected from each participant under aseptic conditions. Serum ferritin was quantified via chemiluminescent immunoassay (CLIA), and HbA1c was measured using high-performance liquid chromatography (HPLC). Data were analyzed in SPSS v.25.0. Continuous variables (e.g., age, HbA1c) were expressed as mean ± standard deviation; categorical variables (e.g., glycemic status) as frequencies/percentages. Pearson's correlation coefficient assessed the relationship between serum ferritin and HbA1c. Confounding variables (age, gender, hypertension, diabetes control, family history, residence, obesity) were controlled via stratification, with post-stratification chi-square tests evaluating their impact on ferritin levels. Statistical significance was set at *p* ≤ 0.05.

Results

This cross-sectional study analyzed 151 patients with type 2 diabetes mellitus (T2DM) to evaluate serum ferritin as a predictive biomarker for glycemic control. The baseline characteristics of participants are summarized in Table I. The mean age was 48.8 ± 10.8 years, with a female predominance (57%, n=86). The mean BMI was 26.9 ± 1.9 kg/m², and 36.4% (n=55) were obese (BMI >27.5 kg/m²). Most participants resided in rural areas (52.3%, n=79). Hypertension was present in 39.7% (n=60), and 69.5% (n=105) reported a family history of hypertension. The median HbA1c was 7.7% (IQR: 3.3), with only 41.1% (n=62) achieving glycemic control (HbA1c <7%). The median serum ferritin level was 96 ng/mL (IQR: 131), and elevated ferritin (>250 ng/mL for males, >120 ng/mL for females) was observed in 30.5% (n=46) of participants.

A weak but statistically significant positive correlation was identified between HbA1c and serum ferritin levels (Spearman's $\rho = 0.252$, *p* = 0.002). Elevated serum ferritin was more prevalent in patients with uncontrolled diabetes (HbA1c ≥7%) compared to those with controlled diabetes (44.9% vs. 9.7%). Similarly, participants with a family history of diabetes exhibited higher frequencies of

elevated ferritin than those without (37.1% vs. 15.2%) (Table II).

Table I: Baseline Characteristics of Study Participants. (n=151)

Characteristic	Value
Age (years), mean ± SD	48.8 ± 10.8
Gender, n (%)	
- Female	86 (57.0%)
- Male	65 (43.0%)
BMI (kg/m²), mean ± SD	26.9 ± 1.9
Obesity (BMI >27.5 kg/m²), n (%)	55 (36.4%)
Residence, n (%)	
- Rural	79 (52.3%)
- Urban	72 (47.7%)
Hypertension, n (%)	60 (39.7%)
Family History of Hypertension, n (%)	105 (69.5%)
HbA1c (%), median (IQR)	7.7 (3.3)
Controlled Diabetes (HbA1c <7%), n (%)	62 (41.1%)
Serum Ferritin (ng/mL), median (IQR)	96 (131)
Elevated Serum Ferritin, n (%)	46 (30.5%)

Stratified analysis revealed persistent positive correlations between HbA1c and serum ferritin across all subgroups (Table III). Significant correlations ($p<0.05$) were observed in females, obese individuals (BMI >27.5 kg/m²), rural residents, non-hypertensive patients, and those without a family history of hypertension.

Table II: Frequency of Elevated Serum Ferritin by Glycemic Control and Family History of Diabetes.

Variable	Category	Elevated Serum Ferritin, n (%)
Glycemic Control	Controlled (HbA1c <7%)	6/62 (9.7%)
	Uncontrolled (HbA1c ≥7%)	40/89 (44.9%)
Family History of Diabetes	Present	39/105 (37.1%)
	Absent	7/46 (15.2%)

Table III: Stratified Analysis of Correlation Between HbA1c and Serum Ferritin Levels.

Subgroup	Spearman's ρ	p-value
Age	0.301*	0.018
Gender		
- Female	0.287*	0.022
- Male	0.198	0.112
Obesity (BMI >27.5 kg/m²)	0.312*	0.015
Residence		
- Rural	0.276*	0.028
- Urban	0.221	0.089
Hypertension		
- Absent	0.293*	0.020
- Present	0.210	0.101
Family History of Hypertension		
- Absent	0.305*	0.017
- Present	0.234	0.075

Discussion

The findings from this cross-sectional study of 151 Pakistani adults with type 2 diabetes mellitus (T2DM) demonstrate a statistically significant positive correlation between serum ferritin and HbA1c (Spearman's $\rho = 0.252$, *p* = 0.002), reinforcing serum ferritin as a predictive biomarker for glycemic control in a South Asian population with high T2DM burden.[14]

The substantially higher prevalence of elevated ferritin in uncontrolled diabetes (HbA1c ≥7%) compared to controlled cases (44.9% vs. 9.7%) underscores its clinical utility for risk stratification. This aligns with pathophysiological evidence linking iron overload to oxidative stress, pancreatic β-cell dysfunction, and impaired insulin secretion, mechanisms particularly relevant in populations like South Asians who exhibit heightened β-cell vulnerability.[15]

The persistence of this correlation after stratification for confounders like age, gender, hypertension, and obesity strengthens the independence of ferritin's association with dysglycemia, though residual confounding from unmeasured variables (e.g., dietary iron intake, subclinical inflammation) cannot be excluded.[16]

Ethnic and regional distinctions emerge when contextualizing these results globally. While the ferritin-HbA1c correlation directionally matches Western and East Asian studies, its magnitude ($\rho = 0.252$) is weaker than correlations reported in those populations.[17]

This attenuation may reflect methodological rigor such as excluding conditions that elevate ferritin (e.g., anemia, infection) or unique population characteristics, including Pakistan's high genetic susceptibility, dietary patterns, and comorbidities. Notably, Pakistan has the world's highest comparative diabetes prevalence (30.8% in 2021, projected to rise to 33.6% by 2045), driven by rapid urbanization, aging demographics, and lifestyle transitions.[18]

The stronger correlation in rural residents ($\rho = 0.276$, *p* = 0.028) may reflect dietary iron bioavailability or inflammation profiles distinct from urban settings, highlighting socioeconomic influences on T2DM phenotypes. Subgroup analyses revealing significant associations in females and obese individuals suggest sex-specific iron metabolism interactions and synergistic effects between iron overload and adiposity. Adipose tissue inflammation potentiates iron-induced

oxidative stress, exacerbating insulin resistance[19], while gender differences may involve hormonal modulation of iron absorption or inflammation.

Mechanistically, hepatic iron accumulation impairs insulin clearance and promotes gluconeogenesis, potentially linking ferritin elevation to metabolic dysfunction-associated steatotic liver disease (MASLD), a common T2DM comorbidity. Iron overload also triggers autophagic dysregulation, which may initially mitigate hepatic lipid accumulation but ultimately accelerates β-cell apoptosis and insulin resistance in advanced T2DM.[20]

This is critical in South Asians, who demonstrate greater β-cell dysfunction relative to insulin resistance than Caucasians [21], rendering them susceptible to glucotoxicity even with moderate ferritin increases. The high frequency of elevated ferritin in participants with a family history of diabetes (37.1% vs. 15.2%) further suggests genetic intersections between iron homeostasis and diabetes risk, possibly involving polymorphisms in hepatocyte nuclear factors (e.g., *HNF4A*) that regulate both iron storage and insulin secretion pathways.[22]

Clinically, these findings advocate integrating ferritin assessment into routine diabetes management in Pakistan, particularly for high-risk subgroups (women, obese, rural dwellers). Early detection of elevated ferritin could prompt interventions such as dietary modification to reduce heme iron intake or phlebotomy trials.[23]

though efficacy requires validation in local populations. Nevertheless, limitations including the cross-sectional design (precluding causal inference), single-center sampling, and modest correlation strength caution against overemphasizing ferritin as a standalone biomarker. Future longitudinal studies should investigate temporal ferritin trajectories and their relationship to β-cell decline, while genetic research could clarify ethnic-specific susceptibility variants. Mechanistic work exploring hepcidin-ferritin axis dysregulation and tissue-specific iron deposition (e.g., in pancreas or liver) would deepen pathophysiological insights.[24]

In conclusion, this study substantiates serum ferritin as an accessible biomarker for glycemic control in Pakistani T2DM patients, with implications for personalized risk assessment and adjunctive management strategies. Its integration into diabetes care protocols may mitigate this population's disproportionate disease burden, projected to escalate with demographic and environmental shifts.

Conclusion

This study showed that serum ferritin is a modest yet statistically significant positive correlation with HbA1c and was markedly higher in patients with uncontrolled glycemia. The association persisted after adjustment for major demographic and clinical confounders, supporting ferritin's potential as an adjunct marker of dysglycemia in South Asian populations where diabetes prevalence and β-cell vulnerability are high. Routine assessment of ferritin could facilitate early risk stratification and targeted interventions, particularly for women, obese individuals, and rural residents. Nonetheless, the cross-sectional design, single-site recruitment, and unmeasured inflammatory covariates limit causal inference; longitudinal, multi-center studies are warranted to confirm temporal relationships and clarify mechanistic pathways before ferritin is fully integrated into diabetes management algorithms.

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