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Original Research Article

Correlation Between Glycated Hemoglobin (HbA1c) and Serum Ferritin Levels in Patients with Type 2 Diabetes Mellitus

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Abstract:

Background: Diabetes mellitus (DM) is a chronic metabolic disorder with an increasing global prevalence, particularly in India. Iron metabolism has been "implicated in the pathogenesis of type 2 diabetes mellitus (T2DM), with evidence suggesting a correlation between elevated serum ferritin levels and impaired glycemic control. Understanding this association could provide novel insights into the metabolic disturbances underlying T2DM.

Objectives: This study aims to evaluate the relationship between serum ferritin levels and glycemic control in T2DM patients, with a specific focus on its correlation with glycated hemoglobin (HbA1c) levels and disease duration.

Methods: A case-control study was conducted at Department of Biochemistry, Patna Medical College, India, including 76 participants (38 T2DM cases and 38 age-matched healthy controls). Serum ferritin and HbA1c levels were measured using Electrochemiluminescence Immunoassay (ECLIA) and Turbidimetric Inhibition Immunoassay, respectively. Data were analyzed using SPSS 27.0, employing Student's t-test and Pearson's correlation.

Results: T2DM patients exhibited significantly higher serum ferritin levels (528.46 ± 142.30 µg/L) compared to controls (178.62 ± 94.75 µg/L) ($p < 0.0001$). A positive correlation was observed between serum ferritin and HbA1c levels ($r = 0.621$, $p < 0.0001$), suggesting that higher ferritin levels are associated with poorer glycemic control. Additionally, a weak but significant correlation was found between serum ferritin and diabetes duration ($r = 0.278$, $p = 0.047$).

Conclusion: Elevated serum ferritin levels are significantly associated with impaired glycemic control and disease progression in T2DM. These findings underscore the role of ferritin as a biomarker for metabolic dysregulation in diabetes management.

Keywords: Glycemic Control, HbA1c, Oxidative Stress, Serum Ferritin, Type 2 Diabetes Mellitus.

Introduction

Diabetes mellitus (DM) is a chronic metabolic and endocrine disorder that has emerged as a significant public health challenge worldwide. The prevalence of diabetes has increased exponentially, reaching pandemic proportions, and affecting both developing and developed nations. India, in particular, has experienced a rapid rise in diabetes cases, earning the dubious distinction of being the world's diabetes capital. The burden of diabetes is further compounded by its association with various comorbidities, including cardiovascular disease, neuropathy, nephropathy, and retinopathy, making it one of the leading causes of morbidity and mortality globally [1,2].

Among the various factors contributing to the pathophysiology of diabetes, iron metabolism has garnered increasing attention. The earliest evidence linking systemic iron overload with abnormal glucose metabolism emerged from observations in patients with hereditary hemochromatosis (HH), who exhibited an increased frequency of diabetes mellitus [3]. Subsequent research has established that iron overload, irrespective of its etiology, plays a crucial role in the development of type 2 diabetes mellitus (T2DM). Two key observations support this association: (a) an increased incidence of T2DM in individuals with excess iron load from various sources and (b) improvement in glycemic control following a reduction in iron levels through phlebotomy or iron chelation therapy [4,5]. These findings suggest that iron overload is not merely an epiphenomenon but an active contributor to diabetes pathogenesis.

Recent studies have further reinforced the link between iron metabolism and glucose homeostasis. Elevated body iron stores have been implicated in

glucose intolerance, gestational diabetes, insulin resistance, and the metabolic syndrome [6]. Insulin resistance is a hallmark of T2DM, characterized by impaired insulin signaling, leading to elevated blood glucose levels. Chronic systemic subclinical inflammation has been identified as a key driver of insulin resistance, with several acute-phase proteins, including serum ferritin, playing a role in metabolic dysregulation and atherosclerosis [7]. High serum ferritin levels have been positively correlated with increased risk of T2DM, suggesting a direct relationship between iron status and glycemic control [8].

The underlying mechanisms through which iron overload contributes to diabetes pathogenesis are multifaceted. One proposed mechanism involves oxidative stress-mediated pancreatic beta-cell dysfunction. Iron, being a transitional metal, has potent pro-oxidant properties, leading to the generation of reactive oxygen species (ROS) that can cause oxidative damage to pancreatic beta cells, impairing insulin secretion [3]. Additionally, iron overload disrupts hepatic insulin extraction and glucose metabolism, further exacerbating hyperglycemia. The hormone hepcidin, which regulates iron metabolism, has also been implicated in diabetes pathogenesis. Chronic inflammation associated with T2DM leads to increased IL-6-mediated hepcidin expression, altering iron homeostasis and contributing to insulin resistance [5].

Glycation of proteins, including hemoglobin, is another significant consequence of chronic hyperglycemia. The formation of Advanced Glycated End Products (AGEs) has been linked to diabetic complications, including microvascular and macrovascular damage [6]. Elevated serum ferritin levels have been associated with poor glycemic control, as indicated by increased glycated hemoglobin (HbA1c) levels in diabetic individuals [7]. This association highlights the potential role of ferritin as a marker of iron overload and metabolic dysregulation in T2DM. Moreover, excessive iron stores may contribute to long-term diabetes complications, necessitating further research to establish optimal serum ferritin thresholds for clinical intervention [8]. Despite mounting evidence linking iron metabolism with diabetes, gaps remain in our understanding of the precise molecular mechanisms underlying this relationship. Further studies are needed to elucidate the optimal ferritin cut-off values for predicting diabetes risk and to explore potential therapeutic interventions targeting iron homeostasis. Understanding the interplay between iron metabolism and glucose regulation" could pave the way for novel strategies in diabetes prevention and management.

Materials and Methods

Study Design and Location: This case-control study was "conducted at Department of Biochemistry, Patna Medical College, Patna, Bihar, India from September 2024 to December 2024.

Study Population

A total of 76 participants were included in the study, divided into two groups:

- **Case Group (n = 38):** Patients diagnosed with Type 2 Diabetes Mellitus (T2DM) for more than one year, aged 30 years and above, recruited from both inpatient and outpatient departments of Medicine. Diagnosis was based on fasting blood sugar (FBS) levels greater than 126 mg/dL and postprandial blood sugar (PPBS) levels exceeding 200 mg/dL.
- **Control Group (n = 38):** Age-matched healthy individuals with no history of diabetes or metabolic disorders.

Patients with a history of hypertension, obesity, renal diseases, liver diseases, valvular heart diseases, smoking, or a family history of diabetes were excluded from the study.

Procedure: After obtaining informed consent, 5 mL of venous blood was collected from each participant under aseptic conditions. The sample was divided into two aliquots: 2.5 mL in a plain tube for serum ferritin estimation and 2.5 mL in an EDTA tube for glycated hemoglobin (HbA1c) analysis. Serum ferritin levels were measured using the Roche Cobas e411 analyzer based on the Electrochemiluminescence Immunoassay (ECLIA) method. HbA1c levels were determined using the Vitros 5600 dry chemistry analyzer employing the Turbidimetric Inhibition Immunoassay method. All biochemical assays were performed following standard operating procedures to ensure accuracy and reproducibility.

Statistical Analysis: Data were analyzed using SPSS version 27.0. Descriptive statistics, including mean and standard deviation, were used to summarize the data. Group comparisons between cases and controls were performed using Student's unpaired t-test. Pearson's correlation coefficient was applied to assess the relationship" between serum ferritin and glycated hemoglobin levels. A p-value of less than 0.05 was considered statistically significant. Results were interpreted to determine the association of ferritin" levels with glycemic control in diabetic patients.

Results

The gender-wise distribution of participants is presented in Table 1. Among the total 76 participants, 45 (59.2%) were male and 31 (40.8%) were "female. In the case group, 24 out of 38 (63.2%) were male, whereas in the control group, 21 out of 38 (55.3%) were male. Similarly, 14 (36.8%)

of the cases and 17 (44.7%) of the controls were female. This indicates a slight male predominance in both groups.

Table 1: Gender-wise Distribution of Participants			
Gender	**Cases (n = 38)**	**Controls (n = 38)**	**Total (N = 76)**
Male	24 (63.2%)	21 (55.3%)	45 (59.2%)
Female	14 (36.8%)	17 (44.7%)	31 (40.8%)
Total	**38 (100%)**	**38 (100%)**	**76 (100%)**

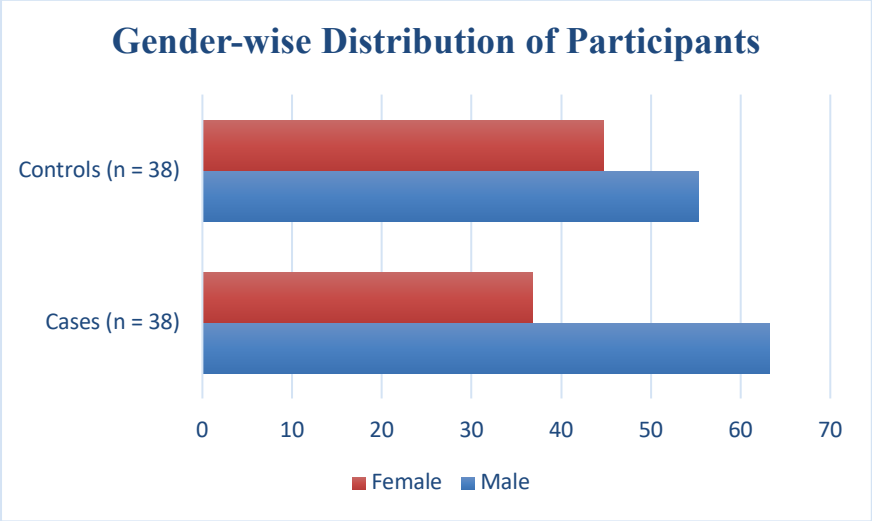

Figure 1: Gender-wise Distribution of Participants

As shown in Table 2, the mean serum ferritin levels were significantly higher in the case group (528.46 ± 142.30 µg/L) compared to the control group (178.62 ± 94.75 µg/L). The difference was found to be statistically significant ($t = 13.98$, $p < 0.0001$). This suggests a strong association between elevated serum ferritin levels and the condition under study, emphasizing its potential role as a biochemical marker.

Table 2: Comparison of Serum Ferritin Levels (µg/L) Between Cases and Controls							
Group	**N**	**Mean (µg/L)**	**Standard Deviation**	**Standard Error Mean**	**t-value**	**p-value**	**Significance**
Cases	38	528.46	142.30	23.07	13.98	<0.0001	Significant
Controls	38	178.62	94.75	15.37			

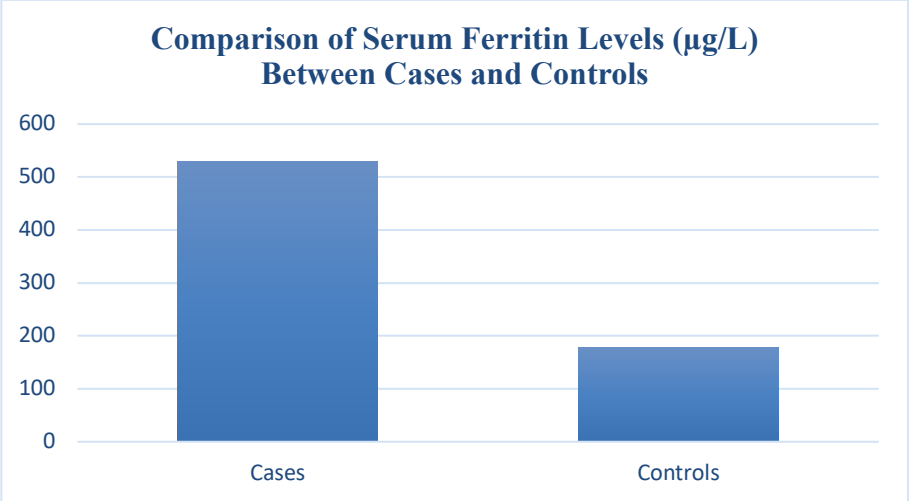

Figure 2: Comparison of Serum Ferritin Levels (µg/L) Between Cases and Controls

The correlation between serum ferritin levels and HbA1c levels is depicted in Table 3. A positive correlation was observed between these two parameters ($r = 0.621$, $p < 0.0001$), indicating that as serum ferritin levels increase, HbA1c levels tend to rise. This suggests a possible link between iron metabolism and glycemic control, reinforcing the role of ferritin as a contributing factor to disease progression.

Table 3: Correlation Between Serum Ferritin Levels and HbA1c Levels

Parameter	Mean	Standard Deviation	N	Pearson's Correlation (r)	p-value	Significance
Serum Ferritin	528.46	142.30	38	0.621	<0.0001	Significant
HbA1c Level	6.72	0.48	38			

Table 4 demonstrates the correlation between serum ferritin levels and the duration of diabetes in the case group. A weak but statistically significant positive correlation was found ($r = 0.278$, $p = 0.047$), suggesting that serum ferritin levels tend to increase with a longer duration of diabetes. Although this correlation is not very strong, it still highlights a potential relationship between chronic disease progression and alterations in iron storage.

Table 4: Correlation Between Serum Ferritin Levels and Duration of Diabetes

Parameter	Mean	Standard Deviation	N	Pearson's Correlation (r)	p-value	Significance
Duration of Diabetes (years)	7.85	3.22	38	0.278	0.047	Significant
Serum Ferritin	528.46	142.30	38			

Overall, the findings indicate that serum ferritin levels are significantly elevated in affected individuals compared to healthy controls, and higher ferritin" levels are associated with poorer glycemic control and a longer disease duration. These results underscore the importance of monitoring serum ferritin as a potential marker for disease progression and metabolic disturbances.

Discussion

The present study investigated the association between serum ferritin levels and glycemic control in individuals with type 2 diabetes "mellitus (T2DM). Our findings "revealed that patients with T2DM exhibited significantly higher serum ferritin levels compared to healthy controls. Moreover, a positive correlation was observed between serum ferritin and glycated hemoglobin (HbA1c) levels, suggesting that elevated ferritin may be linked to poorer glycemic control. Additionally, a weak but statistically significant correlation was found between serum ferritin levels and the duration of diabetes, indicating that ferritin concentrations may increase as the disease progresses.

These results align with previous research highlighting the role of serum ferritin as an indicator of iron status and its potential involvement in glucose metabolism. For instance, a study by Sharifi and Sazandeh (2004) demonstrated that serum ferritin levels were significantly higher in patients with T2DM compared to controls, and there was a positive correlation between ferritin and HbA1c levels [9]. Similarly, Gandhi et al. (2018) reported elevated serum ferritin levels in T2DM patients and a positive association with HbA1c, supporting the notion that increased body iron stores may contribute to insulin resistance and suboptimal glycemic control [10].

The observed association between elevated serum ferritin and T2DM can be attributed to several underlying mechanisms. Iron plays a crucial role in various cellular processes, including oxygen transport and DNA synthesis. However, excessive iron can catalyze the formation of reactive oxygen species, leading to oxidative stress and subsequent damage to insulin-producing β-cells in the pancreas. This oxidative stress may impair insulin secretion and action, contributing to insulin resistance—a hallmark of T2DM. Furthermore, iron-induced oxidative stress can exacerbate chronic inflammation, which is known to interfere with insulin signaling pathways, thereby worsening glycemic control [11].

In our study, the positive correlation between serum ferritin and HbA1c levels underscores the potential of ferritin as a marker for monitoring glycemic control in T2DM patients. This finding is consistent with the work of Afrin et al. (2015), who found a significant positive correlation between serum ferritin and HbA1c levels in T2DM patients, suggesting that higher ferritin concentrations are associated with poorer glycemic control [12]. Monitoring serum ferritin levels in clinical practice could, provide additional insights into the metabolic status of diabetic patients and help identify individuals at risk for complications related to poor glycemic control.

The weak but significant correlation between serum ferritin levels and the duration of diabetes observed in our study suggests that iron accumulation may occur progressively over the course of the disease.

This is in line with findings by Manjula et al. (2016), who reported a positive association between serum ferritin levels and the duration of diabetes, indicating that longer disease duration may be linked to increased iron stores [13]. Chronic hyperglycemia can lead to non-enzymatic glycation of proteins, including ferritin, potentially altering its structure and function, which may contribute to increased ferritin levels over time. Additionally, prolonged exposure to high glucose levels can enhance intestinal iron absorption and promote iron accumulation in tissues, further elevating serum ferritin concentrations [14].

It is important to note that elevated serum ferritin levels may also reflect underlying inflammation, as ferritin is an acute-phase reactant. Chronic low-grade inflammation is a common feature of T2DM and can independently raise serum ferritin levels. Therefore, elevated ferritin in diabetic patients could be a marker of both increased iron stores and inflammation. Distinguishing between these two contributors is essential for accurate interpretation of ferritin levels and for developing targeted therapeutic strategies [15].

The clinical implications of our findings are significant. Elevated serum ferritin levels have been associated with an increased risk of diabetes-related complications, such as cardiovascular diseases and nephropathy. Monitoring ferritin levels in T2DM patients could aid in early identification of individuals at higher risk for these complications, allowing for timely interventions. Moreover, therapeutic strategies aimed at reducing iron overload, such as phlebotomy or iron chelation, have shown promise in improving insulin sensitivity and glycemic control in patients with hereditary hemochromatosis—a condition characterized by excessive iron accumulation. Further research is warranted to explore the potential benefits of such interventions in T2DM patients with elevated ferritin levels [16].

Our study has several limitations that should be acknowledged. The cross-sectional design precludes establishing causality between elevated serum ferritin levels and poor glycemic control. Longitudinal studies are needed to determine whether increased ferritin is a cause or consequence of deteriorating glycemic control. Additionally, we did not assess markers of inflammation, such as C-reactive protein, which could help" differentiate between ferritin elevation due to iron overload versus inflammation. Future studies should incorporate these measures to provide a more comprehensive understanding of the factors contributing to elevated ferritin levels in T2DM patients [17].

Conclusion

In conclusion, our study demonstrates that serum ferritin levels are significantly elevated in individuals with T2DM and are positively correlated with HbA1c levels and the duration of diabetes. These findings suggest that serum ferritin could serve as a valuable marker for assessing glycemic control and disease progression in T2DM patients. Incorporating ferritin measurements into routine clinical practice may" enhance the management of T2DM by identifying patients at risk for poor glycemic control and related complications. Further research is needed to elucidate the underlying mechanisms linking iron metabolism to glucose homeostasis and to evaluate the potential therapeutic benefits of modulating iron levels in T2DM management.

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