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Original Research Article

A Comparative Study of Serum Ferritin and Glycated Haemoglobin in Patients with Type 2 Diabetes Mellitus and Healthy Controls

Divya Khandelwal[1], Alka Meena[2], Arpit Khandelwal[3], Bhawna Bagaria[4], S K Vardey[5]

[1]Senior Resident, Department of Biochemistry, Govt. Medical College, Kota

[2]Assistant Professor, Department of Biochemistry, SMS Medical College, Jaipur

[3]Assistant Professor, Department of Orthopaedics, Jhalawar Medical College, Jhalawar

[4]Assistant Professor, Department of Biochemistry, SMS Medical College, Jaipur

[5]Professor, Department of Biochemistry, SMS Medical College, Jaipur

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Corresponding author: Dr Bhawna Bagaria
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Abstract

Background: Diabetes is a metabolic disorder characterized by hyperglycemia which is associated with rise in hba1c. Serum ferritin is a ubiquitous intracellular protein complex that reflect the iron stores of the body .this study was carried out to find out the relationship between serum ferritin and hba1c in type2 diabetic patients and controls and to see the influence of body iron stores on hba1c and blood glucose.

Materials & Methods: After taking necessary permissions, a cross sectional study was conducted at Department of Biochemistry and Department of Endocrinology, SMS Hospital, Jaipur. This study includes 31 patients suffering from type 2 diabetes aged 30-80 years compared with 31 controls. Hba1c was measured by latex turbidimetric method and serum ferritin was assessed by CLIA (chemiluminescence).

Results: Results were analyzed statistically by Student's t-test, Pearson correlation coefficient test. Mean serum ferritin was significantly higher in diabetics than in the control group (177.3±49.14 µgm/L vs. 94.9±55.59 µgm/L, $p<0.001$). There was statistically highly significant ($p <0.001$) positive correlation between serum ferritin and HbA1c in diabetic patients ($p<0.001$).

Conclusion: The findings of this study concludes that serum ferritin is elevated in patients with type 2 diabetes mellitus when compared to healthy controls and it indicates that ferritin can be used as a marker for glycemic control in diabetic patients because Hba1c may be affected by a variety of genetic, hematological diseases (haemoglobinopathies), certain type of anemia, and disorders associated with accelerated red cell turnover such as tumors.

Keywords: Diabetes Mellitus (DM), Glycated haemoglobin (Hba1c), ferritin

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Background

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia either due to insulin resistance or impaired insulin secretion, results from a combination of environmental and genetic factors [1].

The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system [2].

In 2020, according to the latest edition of the international diabetes federation (IDF) diabetes atlas shows that 463 million adults are currently living with diabetes in the world and 88 million people in the southeast asia region. Of this 88 million people, 77 million belong to India. Based on current trends the international diabetes federation (IDF) estimates that there will be 578 million individuals will have diabetes by the year 2030, and 700 million by 2045 [3,4].

Although the prevalence of both type 1 and type 2 DM is increasing worldwide, but prevalence of type 2 DM is rising much more rapidly, probably because of increasing obesity, reduced activity levels as countries have become more industrialized, and ageing of the population [5].

So it is important to research over new useful aspects and disease entities. It is recently recognized that increased body iron stores are associated with the development of glucose intolerance, type 2 DM and insulin resistance syndrome. Some researches had shown that, there is difficult control of hyperglycemia in patients with iron overload.

The etiopathogenesis of type 2 diabetes is multi-factorial and recently the body iron levels are being implicated in its causation. The role of iron in the pathogenesis of diabetes is suggested by**:-**

An increased incidence of type 2 diabetes in diverse causes of iron overload.

Reversal or improvement in diabetes (glycemic control) with a reduction in iron load achieved using either phlebotomy or iron chelation therapy. Recently, correlation has been established between increased dietary iron intake, particularly eating red meat and increased body iron stores, and the development of diabetes. A causative link with iron overload is suggested by the improvement in insulin sensitivity and insulin secretion with frequent blood donation and decreased iron stores [6].

Plasma ferritin levels are considered to be an indicator of body iron stores. Ferritin is one of the key proteins that play an important role in regulating iron homeostasis.

It is found in most tissues as a cytosolic protein, but small amounts are secreted into the serum where it functions as an iron carrier. Plasma ferritin is also an indirect marker of the total amount of iron stored in the body.

Increased ferritin may induce diabetes through a variety of mechanisms including oxidative damage to pancreatic beta cells (insulin deficiency) because low expression of the antioxidant defense system [7]. A high expression of divalent metal transporter additionally predisposes them for more accumulation of iron than other cells and potentiates the danger from iron catalyzed oxidative stress [8], impairment of hepatic insulin extraction by the liver(hepatic dysfunction) and interference with insulin's ability to suppress hepatic glucose production (insulin resistance) [9].

Raised Serum Ferritin may possibly be related to the occurrence of long term complications of diabetes, both micro vascular and macro vascular The complications of diabetes mellitus are influenced not only by the average level of

blood glucose along with glycated haemoglobin but also by ferritin [10].

Hemoglobin A1C (HbA1c) or glycated hemoglobin is the predominant fraction of hemoglobin A. It is used as the gold standard method for assessing the glycemic control. It reflects the glycemic status of the individual over the past 3 months. It is formed by glycation ofNH2-terminal valine of the hemoglobin β chain [11].

According to the guidelines of American Diabetic Association, the target HbA1c in all diabetic patients is below 7%, to prevent the development of secondary microvascular complications. Similar to plasma glucose, HbA1c level is related to the prevalent retinopathy [12].

Measurement of HbA1c therefore provides valuable information for management of diabetes mellitus but HbA1c may be affected by a variety of genetic, haematologic and illness-related factors (haemoglobinopathies), certain types of anemia, and disorders associated with accelerated red cell turnover such as malaria [13].

Overall there is paucity of literature especially from India showing direct evidence of relation between Diabetes Mellitus and iron overload. Thus, research has been designed to enlighten this path and to find association of elevated serum ferritin level with Diabetes mellitus type 2 and its correlation with glycated haemoglobin which may help to understand the significance of ferritin for the better management of type 2 diabetes mellitus.

Materials and Methods

After taking Necessary permission from the institute ethical committee and Department of endocrinology, the study was conducted at Central Lab, Department of Biochemistry and endocrinology OPD SMS Medical College and hospital, Jaipur. This study was a Hospital based comparative Cross sectional study and sampling for the study was done from period of January 2020 to November 2020. An informed written consent was obtained from the patients and controls. 31 patients aged 30-80 years were suffering from type 2 diabetes since > 2 years diagnosed and confirmed according to World Health Organization criteria (FBS ≥126 mg/dl & 2 hour plasma glucose ≥ 200 mg/dl). Age matched healthy individuals (relatives/attendants of patient and hospital staff) who were willing to participate in the study giving written consent were taken as controls.

Patients with the following condition: Type 1 DM, Hemolytic anaemia, iron deficiency anaemia, Haemoglobinopathies and bleeding disorders, Pregnancy, Chronic liver disease, altered serum ferritin like haemochromatosis, patient with repeated blood transfusion were excluded.

Selection of subject was based on inclusion and exclusion criteria, age and sex matched controls and cases were included in the present study after obtaining informed consent. A proforma was used to record relevant information and patient's data. 4 mL of venous blood was collected in plain vacutainer, ferritin were analyzed by Chemiluminescence immuno assay and 2 mL into EDTA containing vacutainer for Hba1c Assay by turbidimetry**.**

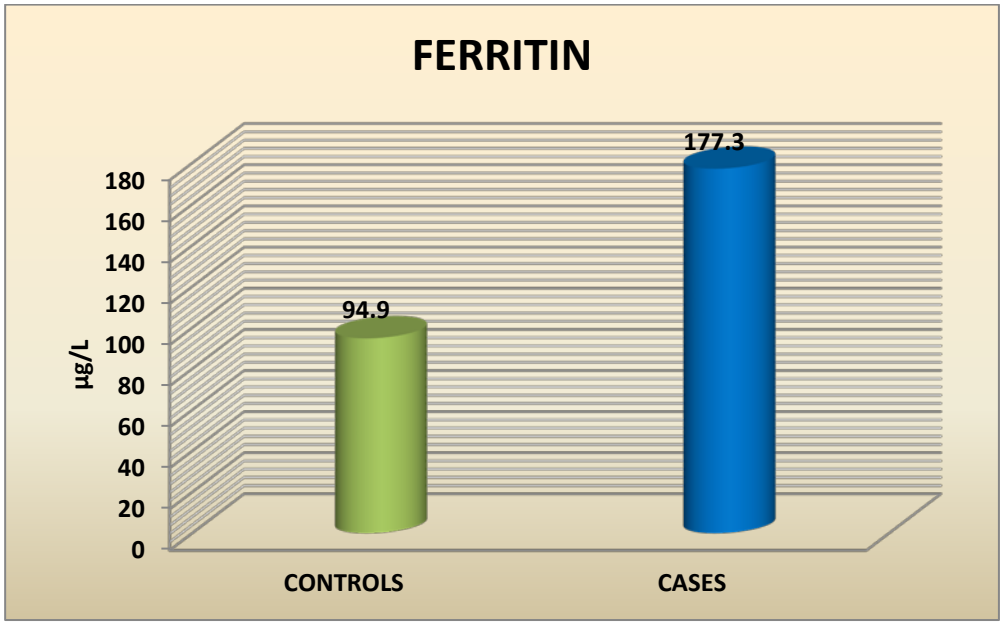
Results

The characteristics of the studied population, including age, the mean levels of blood sugar and HBA1c are shown in Table 1

Table 1: Statistical Indices of the study

Test/ Parameters	Controls	Cases	P value
Age (years)	57.6 ± 9.75	54.9 ±10.87	0.158 (NS)
Fasting Blood Glucose (mg/dl)	83.0 ± 4.24	135.3 ± 17.04	<0.001 (S)
Post Prandial Glucose (mg/dl)	128.3 ± 5.60	210.5 ± 42.45	<0.001 (S)
HBA1C (%)	5.2 ± 0.19	8.6 ± 1.47	<0.001 (S)
Hemoglobin (g/dl)	13.1 ± 0.64	13.3 ± 1.18	0.173 (NS)
Ferritin (µg/L)	94.9 ± 55.59	177.3 ± 49.14	<0.001 (S)

HBA1C and Serum Ferritin: The mean ferritin levels in cases (177.3 ± 49.14 µg/L is more as compared to controls (94.9 ± 55.59 µg/L) and this difference has been found as statistically highly significant (p <0.001) as shown in Table 1 and Graph 1.



Graph 1: Comparison of Mean Ferritin between Controls and Cases

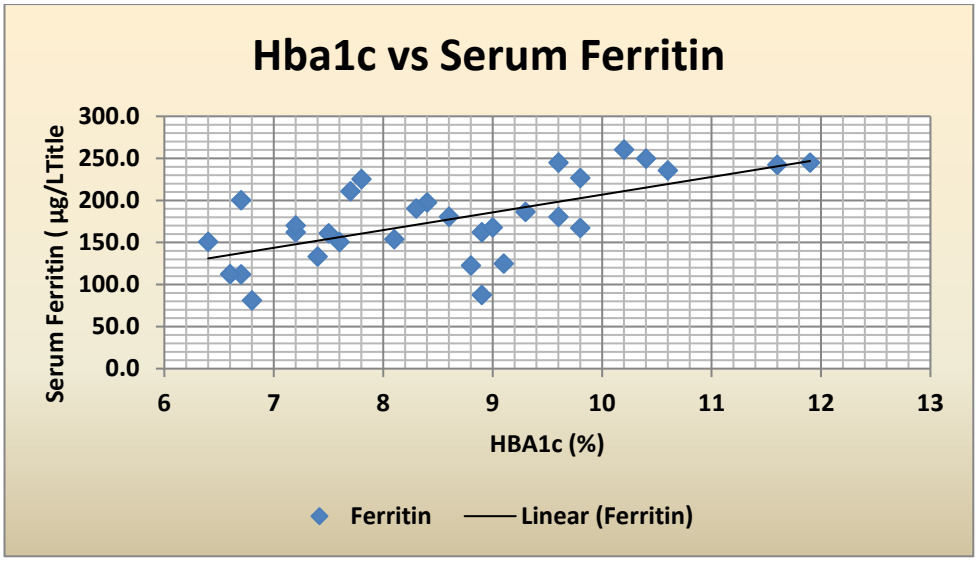
Statistical Correlation between HBA1C and Serum Ferritin

Table 2: Statistical Correlation between HBA1C and Serum Ferritin

Parameter	P value	R Score	R^2	Significance
HBA1C vs Serum Ferritin	.000156	0.6278	0.3941	S

*Data analysis using Pearson correlation analysis

As shown in the above table, when Pearson correlation was applied to compare serum ferritin and HbA1C in diabetes patients ,there is positive linear correlation between mean HbA1C and serum ferritin and it is statistically highly significant (p=0.000156).



Graph 2: Pearson correlation between HBA1C and Serum Ferritin

Discussion

This comparative cross sectional observational study was conducted to assess serum ferritin and HbA1C in the patients who had come for treatment of uncontrolled diabetes and compare with healthy controls, and to find out a correlation, if any. It has been found that ferritin is elevated in diabetic patients

Mean serum ferritin in cases was significantly higher in all age group cases compared to respective controls ($p<0.001$)

This study showed that although serum ferritin was in normal range value, it was at the higher side of normal range in type 2 diabetes patients than in controls and was statistically significant.

Similar findings were reported by, Pramiladevi R *et al*. in 2013 [14] showed that although serum ferritin was in normal range value, it was at the higher side of normal range in type 2 diabetes patients than in controls and was statistically significant. She also got a positive relation between serum ferritin level and duration of diabetes.

Suvarna *et al* [15] from India reported similar indirect evidence that insulin resistance sets in early and correlate well with total units of blood transfused and serum ferritin in chronically transfused patients of thalassemia major.

Although the exact mechanism for association of elevated serum ferritin with type 2 diabetes mellitus is yet not to be established, there are a number of prevailing theories. Increasing concentration of ferritin in cells could cause resistance to insulin and dysfunction of β cells of pancreases.

It is likely to be mediated by three key mechanisms: 1) insulin resistance, 2) insulin deficiency, 3) hepatic dysfunction. An understanding of the pathogenic pathways of iron-induced diabetes is derived mainly from studies on animal models of hemochromatosis. The crucial role of iron in the pathophysiology of disease is derived from the easiness with which iron is reversibly oxidized and reduced. This property, while essential for its metabolic functions, makes iron potentially hazardous because of its ability to participate in the generation of powerful oxidant species such as hydroxyl radical.

The catalytic iron converts poorly reactive free radicals like hydrogen peroxide (H2O2) into highly reactive ones such as hydroxyl radical and superoxide anion that can initiate and propagate the cascades

leading to oxidative damage. These free radicals are powerful pro-oxidants which cause lysis of the lipid cellular membrane, damage the configurational harmony of proteins, and displace nucleic acids in genes. Thus, the catalytic action of free iron is instrumental to insulin resistance in the beginning and later on to reduced insulin release, which subsequently results in the development of T2DM [16].

Table 2 show that there is positive linear correlation between HbA1C level and serum ferritin. It was statistically significant (p=0.000156),(r =0.6278).

Jiang *et al* [17] have reported increase in hydroxyl radical in iron overload which causes cell damage and leads to insulin resistance. Deferroxamine, a chelating agent with antioxidant properties improve fasting blood glucose in chronically transfused patients of thalassemia major support this hypothesis.

In 2007, Jehn M.L *et al* [18] conducted a case-cohort study to determine the association between plasma Ferritin level and risk of type 2 diabetes mellitus. They measured fasting glucose, fasting insulin & serum ferritin. They found that elevated ferritin confer a moderately increased risk of type 2 diabetes.

It was surmised from the study that increased Serum Ferritin levels are associated with insulin resistance, poor glycaemic control and also associated with complications of type-2 DM like nephropathy, retinopathy, neuropathy and hypertension.

Long-standing diabetic co-morbidities are also moderated by iron-mediated deterioration Elevated iron stores could enhance oxidation of lipids, especially of free fatty acids; through accelerated production of free radicals. The complex process of advanced glycation end product formation produces reactive oxygen species (ROS) by metal catalyzed reactions [19].

Advanced glycation end products themselves bind transition metals, potentiating their toxic effects, including insulin resistance. ROS interfere with insulin signaling at various levels, impairing insulin uptake through a direct effect on insulin receptor functions and inhibiting the translocation by GLUT4 in the plasma membrane. Iron through Fenton's reaction participates in the formation of ROS can stimulate vascular smooth muscle cell growth and proto-oncogen expression. Oxidative stress induces both insulin resistance by decreasing internalization of insulin and increased ferritin synthesis [20].

Thus, higher levels of ferritin might be associated with HbA1C and might play a preventive role in diabetes patients.

Conclusion

Two important observations were found in this study. First observation was that, significantly elevated ferritin was found in type 2 diabetic patients when compared to non-diabetic control of the same age group. Second observation was that elevated ferritin in diabetic patient was positively correlated with HbA1c.

Ferritin is the marker of iron overload and has a role in insulin resistance. Thus serum ferritin can be considered as routine diabetic biomarker and measures should be taken to decrease iron load in diabetic patients to improve glycemic control and to prevent development of cardiovascular disease and metabolic syndrome because increased iron storage causes organ damage and worsening of insulin resistance.

References

1. Alvin CP. Diabetes mellitus,19th edition Harrison's principles of Internal medicine; Diagnosis, classification, and pathophysiology chapter 417-page 2399
2. The Diabetic control and complication trial research group the effect of intensive treatment of diabetes on the

development and progression of long term complication in insulin dependent diabetes mellitus N.Eng j Med 329,977-986

3. Whiting Dr, Guariguata L, Weil C, Shawj. IDF Diabetes atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract. 2011; 94:311–21.
4. Anjana RM, Ali MK, Pradeepa R, Deepa M, Datta M, Unnikrishnan R, Rema M, Mohan V. The need for obtaining accurate nationwide estimates of diabetes prevalence in India - rationale for a national study on diabetes. Indian J Med Res. 2011; 133:369–80.
5. Valdez R, Liu T, Yoon PW, Khoury MJ. Family history and prevalence of diabetes in the U.S. population. Diabetes Care 2007; 30: 2517-22.
6. Fernandez Real JM, Penarroja G, Castro A, et al. Bloodletting in high-ferritin type 2 diabetes: effects on insulin sensitivity and β-cell function. Diabetes 2002; 51:1000- 1004.
7. Fernandez Real JM, Penarroja G, Castro A, et al. Bloodletting in high-ferritin type 2 diabetes: effects on insulin sensitivity and β-cell function. Diabetes 2002; 51:1000- 1004.
8. Fernandez-Real JM, Lopez-Bermejo A, Ricart W: Crosstalk between iron metabolism and diabetes. Diabetes. 2002 Aug;51(8):2348-2354.
9 Fernandez Real JM, Ricart W, Arroyo E, et al. Serum ferritin as a component of the insulin resistance syndrome. Diabetes Care 1998; 21:62-68.98
10 Kaye TB, Guay AT, Simonson DC. Non-insulin-dependent diabetes mellitus and elevated serum ferritin level. J Diabetes Complications 1993; 7:246-9.
11 John, Garry, Emma English, and Elise Milosevich. "In Vitro Determination of Hemoglobin A1c for Diabetes Diagnosis and Management: Technology Update." Pathology and Laboratory Medicine International PLMI (2014): 21
12 American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33(Suppl. 1): S62–S69.
13 Bae JC, Suh S, Jin SM, et al. Hemoglobin A1c values are affected by hemoglobin level and gender in non-anemic Koreans. J Diabetes Investig. 2014;5(1):60
14 Dr. Pramiladevi. R, Dr. Umakanth Boke, Dr. Shreeram Kora. Serum ferritin in type 2 diabetes patients. Sch. J. app. Med. Sci.2013 1(5): 472-475
15 Suvarna J, Ingle H, Deshmukh CT. Insulin resistance and beta cell function in chronically transfused patients of thalassemia major. Ind Pediatr 2006; 43:393-400
16 Wolff SP. Diabetes mellitus and free radicals. Free radicals, transition metals and oxidative stress in the aetiology of diabetes mellitus and complications. Br Med Bull. 1993;49(3):642–652
17 Jiang R, Manson JE, Meigs JB, Ma J, Rifai N, Hu FB. Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. JAMA 2004; 291: 711-17
18 Jehn M, Clark JM & Guallar E. Serum ferritin and risk of the meta- bolic syndrome in US adults. Diabetes Care 2004 27 2422–2428.
19 Wolff SP. Diabetes mellitus and free radicals. Free radicals, transition metals and oxidative stress in the aetiology of diabetes mellitus and complications. Br Med Bull. 1993;49(3):642–652
20 Oberley LW. Free radicals and diabetes. Free Radic Biol Med. 1988;5(2):113–124.