ORIGINAL RESEARCH PAPER

General Medicine

CORRELATION BETWEEN SERUM FERRITIN AND GLYCEMIC CONTROL IN PATIENTS OF TYPE 2 DIABETES MELLITUS

KEY WORDS: Diabetes Mellitus, Ferritin, HbA1c, Inflammation, Iron

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ABSTRACT

Introduction: T2DM and its link with inflammation has been researched in recent times. There is also evidence of interaction between glucose homeostasis and iron metabolism. Some studies show that serum ferritin, an acute phase reactant and indicator of body iron stores, is associated with glucose intolerance, T2DM as well as micro and macro vascular complications of diabetes. This study was carried out to evaluate the relationship between serum ferritin and glycemic status in diabetic patients.

Materials and Methods: 100 individuals with type 2 diabetes (M: F=48:52, mean age 56.08 ± 9.52 years, BMI 24.85 ± 4.03 kg/m2), who visited a tertiary care hospital, and 100 age and gender matched controls were included. Exclusion criteria included the factors affecting serum ferritin levels like anaemia, chronic liver or kidney disease. Serum ferritin, HbA1c, FBS, PPBS were measured.

Results: The mean Serum ferritin was significantly higher ($p<0.01$) (189.61 ± 156.99 ng/ml) in diabetic patients when compared to controls (88.74 ± 47.28 ng/ml). Serum ferritin had a positive correlation with HbA1c (r=0.85), FBS (r=0.91) and PPBS (r=0.77). Serum ferritin was significantly related to diabetes duration ($p<0.05$).

Conclusion: Diabetics have elevated ferritin levels which correlate with their glycemic status (HbA1c, FBS, PPBS). It may thus be used as a marker for glycemic control in diabetes.

INTRODUCTION

Diabetes Mellitus (DM) is a clinical syndrome characterised by hyperglycemia caused by absolute or relative deficiency of insulin. DM refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Depending on the etiology of DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization and increased glucose production [1]. 425 million people worldwide, and 8.8% of India's population suffers from diabetes and this is estimated to reach 11.4% by 2045 [2].

It is now known that inflammation contributes to insulin resistance and insulin insufficiency, and thus has a role in diabetes [3, 4]. Ferritin is a complex globular protein that stores iron as soluble and non-toxic component. Increasing concentration of iron and ferritin in cells can cause resistance to insulin and dysfunction of cells of pancreas [5].

The relationship between T2DM and iron metabolism has gained interest in both research and clinical practice. Scientific evidences have predicted influences of elevated serum ferritin levels on insulin resistance and T2DM either because of increased body iron stores or influenced by several inflammatory diseases [6, 7]. Thus, it is postulated that circulating levels of ferritin, also an acute phase reactant, are not truly reflective of body iron stores but may reveal other processes such as systemic inflammation [8, 9].

However, the role of serum ferritin as a marker of iron overload in pancreatic damage and peripheral insulin resistance is not clear. Inconsistent results have been obtained for the correlation of serum ferritin with diabetes mellitus in various studies worldwide. This study was carried out to evaluate the relationship between serum ferritin and glycemic status in diabetic patients.

MATERIALS AND METHODS

This observational study was carried out in the Department of Internal Medicine in Shri Guru Ram Rai Institute of Medical and Health Sciences and Shri Mahant Indiresh Hospital, Dehradun and included 100 subjects with type 2 diabetes mellitus. The study was carried out between December 2017 and November 2019. Diabetes mellitus was diagnosed as per the latest ADA criteria [10]. 100 age and gender matched controls were also included.

Plasma glucose was measured by glucose oxidase-peroxidase method, HbA1c by ion-exchange resin method and serum ferritin was assessed by Chemiluminescence method using Vitros 5600.

Inclusion Criteria-

1. All cases of type 2 diabetes mellitus more than 30 years of age

Controls- Age and gender matched normal healthy subjects (free from any ailment which could affect the parameters under study)

Exclusion Criteria-

1. Anemia of any cause- Hb < 12g/dl in males and Hb <11g/dl in females
2. Chronic liver disease
3. Chronic kidney disease
4. On corticosteroid therapy
5. Overt thyroid dysfunction
6. On iron supplementation
7. Type 1 DM
8. Severe infections, major operations, trauma, critically ill patients admitted in intensive care units
9. History of blood transfusion in the past one year

Statistical Analysis-

Analysis was done using SPSS software. Mean values and standard deviations were calculated for various parameters in both study groups. Students t test was used for comparison of quantitative variables. Correlation between serum ferritin and HbA1c, FBS and PPBS in patients was evaluated using Pearson correlation coefficient. All tests were considered statistically significant if the p-value was <0.05.

RESULTS

Table 1) Inter-group sex distribution of cases studied

Sex	Case Group (n=100)		Control Group (n=100)		p-value
	n	%	n	%	
Male	48	48.0	55	55.0	0.4
Female	52	52.0	45	45.0	
Total	100	100.0	100	100.0	
p-value <0.05 is statistically significant.					

Table 1 shows that out of 100 cases studied in Case Group, 48 (48.0%) were males and 52 (52.0%) were females. Of 100 cases studied in Control Group, 55 (55.0%) were males and 45 (45.0%) were females. Distribution of sex among of cases studied did not differ significantly between two study groups (p-value>0.05).

Figure 1) Age distribution of cases and controls

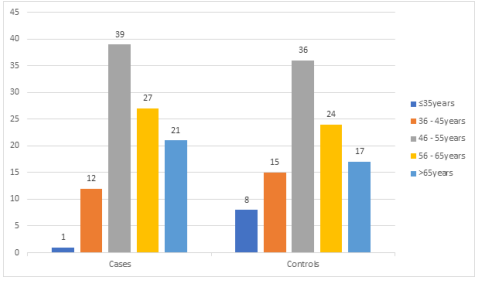

Figure 1 shows the maximum percentage of subjects were in the age group of 46-65 years in both cases and controls

Table 2) Comparison of characteristics among cases and control

Variable	Cases	Controls	p-Value*
	Mean ± SD	Mean ± SD	
Age (years)	56.08 ± 9.52	53.59 ± 11.95	>0.05
Serum Ferritin (ng/ml)	189.61 ± 156.99	88.74 ± 47.28	<0.05
HbA1c (%)	9.65 ± 2.62	5.09 ± 0.44	<0.05
FBS (mg/dl)	199.95 ± 82.28	90.55 ± 6.19	<0.05
PPBS (mg/dl)	265.77 ± 95.74	123.03 ± 9.41	<0.05
BMI (kg/m^2)	24.85 ± 4.03	24.40 ± 2.63	>0.05

Table 2 shows that the serum ferritin, HbA1c, FBS and PPBS were higher among cases as compared to controls, and this was statistically significant. Age, Hb and BMI were similar in the two groups.

Table 3) Comparison of S. ferritin levels according to FBS range among cases

FBS Level (mg/dl)	S. Ferritin (ng/ml)	p-Value*
	Mean ± SD	
101 – 126	57.82 ± 29.74	<0.05
127 – 150	83.99 ± 24.52	
150 – 200	143.38 ± 54.12	
201 – 250	221.23 ± 46.59	
>250	414.29 ± 174.25	

Table 3 shows that the mean ferritin was highest with fasting blood sugar more than 250, followed by 201-250, 150-200, 127-150, 101-126 mg/dl and this difference was found to be statistically significant.

Table 4) Comparison of S. ferritin levels according to HbA1c range among cases

HbA1c (%)	S. Ferritin (ng/ml)	p-Value*
	Mean ± SD	
<6.5	39.49 ± 9.20	<0.05
6.5 – 9	94.88 ± 36.33	
9 – 12	227.38 ± 82.65	
>12	405.21 ± 185.54	

Table 4 shows that the mean ferritin was highest with HbA1c more than 12, followed by 9-12, 6.5-9, less than 6.5% and this difference was found to be statistically significant.

Table 5) Correlation of S. Ferritin with different variable among cases

Variable	Cases	
	Pearson Correlation	p-Value
FBS	0.91	<0.05
PPBS	0.77	<0.05
HbA1C	0.85	<0.05

Table 5 shows that Pearson Correlation of serum ferritin with FBS, PPBS, HbA1c are statistically significant

Figure 2) Correlation of Serum ferritin with HbA1c

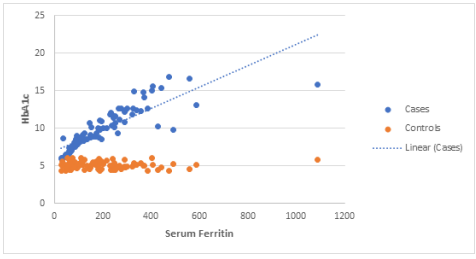

Table 6) Comparison of S. ferritin levels according to Duration of DM range among cases

Duration of DM (years)	S. Ferritin (ng/ml)	p-Value*
	Mean ± SD	
Newly diagnosed	131.09 ± 80.17	<0.05
<5yrs	145.29 ± 105.82	
5 – 10yrs	196.75 ± 130.89	
11 – 15yrs	296.86 ± 266.75	
>15yrs	291.56 ± 191.76	

Table 6 shows that mean ferritin was highest with duration of diabetes between 11-15 years, followed by more than 15, 5-10, less than 5 years and newly diagnosed cases. This difference was statistically significant.

DISCUSSION

The comparison of characteristics studied in our study population of 200 including 100 cases and 100 controls is shown in Table 2. The mean age of our case group was 56.08 ± 9.52 years, which is in accordance with other studies. Thanna RC et al (2016) had mean age of cases 54.5 ± 8.5 years [11] and Pramiladevi et al conducted a study with mean age of 55.5 ± 9.7 years [12]. Majority of patients in the study were in the fifth to seventh decade of life, i.e. from age group 46 to 55 years (39%) and 56 to 65 years (27%) as seen in Figure 1. According to the DECODA Study Group, diabetes mellitus peaks at 60–69 years of age followed by a decline at the 70 years of age in Indian subjects [13]. But in a study by Maheshwari AV et al (2015) the mean age was less [14].

In the present study, the male to female ratio was comparable, with 48% males and 52% females (Table 1). There are studies which have female preponderance. Petchiappan V et al had 57% females as cases [15] while Sharifi F et al study had 61.85% females [16].

The serum ferritin levels in our study among cases was 189.61 ± 156.99 ng/ml (Table 2) which was significantly higher than the controls (p<0.01). Arora P conducted a study in 2017 which revealed mean serum ferritin of 198.37 ± 54.78 ng/ml in diabetics compared to controls (p<0.05) [17]. Similar to our study, the studies by Raj S et al and Thanna R C et al (142 ± 16.2 ng/ml) had significantly higher serum ferritin in diabetic patients than controls [18, 11]. Gandhi S J et al study in Pune (199 ± 32.66 ng/ml) and R Pramiladevi et al in Karnataka, patients with type 2 diabetes mellitus had significantly higher serum ferritin level when compared to the normal [19, 12].

Mean serum ferritin in a study conducted in Iran by Sharifi F et al in 2004 and by Padmaja P et al (2015) in India showed serum ferritin was higher in diabetics compared to controls ($p<0.05$) [16, 20]. A study conducted by Maheshwari AV et al (319.7 ± 133.6 ng/ml) in Gujarat, India and by Alam F et al in Pakistan (233.11 ± 43.84 ng/ml) both had mean ferritin levels in diabetics much higher than our study [14, 21]. The glycemic control in the studies were poor with FBS values much higher than ours.

Increased serum ferritin may be associated with diabetes through a variety of mechanisms including oxidative damage to pancreatic beta cells, impairment of hepatic insulin extraction by the liver and interference with insulin's ability to suppress hepatic glucose production [22, 23]. Exact mechanisms are not clear but it may be explained in two ways. Firstly, iron stores in the pancreas may lead to defective synthesis and secretion of insulin [24]. Secondly, iron deposition culminates in hyperinsulinemia due to obstruction in the insulin withdrawing ability of the liver [25]. Such deposits hinder insulin action, resulting in insulin resistance, which suppresses the yield of glucose in the liver [26]. Poor glycaemic control is the root cause of escalated protein glycation—especially haemoglobin, which restores the free state of iron. This amplified free iron pool revitalizes oxidant generation, conferring damage to biomolecules and leading to complications [27]. Iron overload has been hypothesized to induce insulin resistance by catalyzing oxidative stress [28, 29]. Reactive oxygen species have been implicated in IR pathogenesis on the basis of two types of indirect evidence [29-31].

In our study there was a significant positive correlation between Serum ferritin and HbA1c ($r=0.85$, $p<0.05$), Serum ferritin and FBS ($r=0.91$, $p<0.05$), Serum ferritin and PPBS ($r=0.77$, $p<0.05$) (Table 5, Figure 2). This is important as this points to the role ferritin can play in the future to predict conversion from prediabetes to frank diabetes. These findings were supported by Borah M et al in Northeast region of India, whose ferritin and HbA1c strongly correlated ($r=0.89$) positively, very similar to our study [32]. A central India study by Gandhi SJ et al (2018) demonstrated positive correlation of serum ferritin with HbA1c, FBS and PPBS [33]. In the present study, this positive correlation indicates hyperglycemia causing increased glycation of haemoglobin and increased release of free iron from glycated proteins like haemoglobin. This makes a vicious cycle of hyperglycemia, glycation of haemoglobin and increase in levels of free iron and ferritin. This increased iron pool will enhance oxidant generation leading to damage of biomolecules [34]. However, no correlation was found in studies by Sharifi F et al and R Pramiladevi at al [16, 12].

Our study revealed significant increase in mean ferritin with duration of diabetes ($p<0.05$) (Table 6). This was also observed by Arora P, Raj S et al and Moczulski DK et al. [17, 18, 35].

From the present study, it seems likely that increased ferritin reflects both, the involvement of inflammation, and independent actions of body iron. Elevated ferritin levels without evident iron overload may affect glucose homeostasis, leading to insulin resistance in conjunction with inflammatory changes. The study had a limitation of small sample size and there was no follow up was done.

It can thus be concluded that serum ferritin correlates with glycemic control, i.e., poor the control, higher the serum ferritin levels in diabetic patients. But the issue arises whether to routinely assess serum ferritin as a marker for glycemic control in diabetes or even prediabetes. Though our study is a pointer in that direction, we recommend further large-scale, long-term, prospective studies in different regions of the world before suggesting to include serum ferritin either alone or in combination with HbA1c as a marker for diabetes mellitus.

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