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## RESEARCH ARTICLE

# A STUDY ON RELATION BETWEEN SERUM FERRITIN AND GLYCATED HEMOGLOBIN IN TYPE 2 DIABETES MELLITUS

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**ABSTRACT**

**Background:** Diabetes Mellitus is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism. DM is associated with several complications. Ferritin is the major iron storage protein and plays a key role in iron metabolism. Ferritin in the circulation is a secretory form of the protein which is glycosylated and has been hypothesized for its role in the pathogenesis of diabetes and its complications. Increased accumulation of iron affects insulin synthesis and secretion from the pancreas, and interferes with the insulin extracting capacity of the liver. Iron deposition in muscle decreases glucose uptake because of muscle damage. Iron deposition in the liver may also cause insulin resistance by interfering with the ability of insulin to suppress hepatic glucose production.

**Aim:** This cross-sectional study was performed to find a link between serum ferritin and type 2 diabetes mellitus and also glycated hemoglobin as a blood glucose control marker in diabetic patients.

**Material and Methods:** This study was conducted in the Department of Medicine, BLDE University's Shri B M Patil Medical College and Research Centre, Vijayapura from January 2014 to June 2015 on newly detected and known patients of type 2 diabetes mellitus who attended outpatient and inpatient department. A total of 131 patients of type 2 diabetes mellitus were included in the study. The mean age of study population was 53.46 ± 10.74 years. Out of 131 patients 70 patients (53.43%) were males and 61 patients (46.56%) were females, accounting for a ratio of male to female as 1.15:1. The mean duration of diabetes was 7.04 ± 3.25 years. 105 patients (80.16% of the cases) were on Oral Hypoglycemic Agents for the treatment of diabetes. The mean BMI was 23.95 ± 3.15. 42 patients (32.08% of the cases) had BMI ranging from 25 to 29.99. We observed 90 patients (69%) had fasting blood glucose above 126mg/dl and 72 patients (55%) had post prandial blood glucose above 200mg/dl, showing the existence of poor glycemic control. The mean HbAlc level was 8.34± 0.84. Total cholesterol more than 200 mg/dl in 52 patients (40%) and 67 patients (51%) had LDL Cholesterol more than 100 mg/dl. 62 patients (47%) HDL Cholesterol was less than 40 mg/dl. Triglyceride levels were more than 150 mg/dL in 39 patients (29.77%). 74.7% of cases had serum ferritin ranging from 101 – 200 ng/ml. We found that in 90 patients whose FBS was more than 126mg/dl, the mean serum ferritin was 164.56ng/ml. We found 72 patients whose PPBS was more than 200mg/dl, the mean serum ferritin was 173.49ng/ml. We found 76 patients whose HbAlc was more than 8%, the mean serum ferritin was 176.06ng/ml. The p-value of ≤ 0.001 when we correlated serum ferritin levels with FBS and PPBS and HbA1C. This p value was statistically significant.

**Conclusion:** There was positive association between serum ferritin and body mass index measurements, fasting blood glucose levels, postprandial blood glucose levels, glycosylated hemoglobin as a measure of glycemic control. We also observed there was direct association between serum ferritin levels and triglyceride and LDL Cholesterol, but inverse association with HDL Cholesterol. When correlated with other variables like age, gender, duration of diabetes, total cholesterol, we found no significant correlation (p-value being statistically insignificant).



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## INTRODUCTION

Diabetes Mellitus is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. Diabetes mellitus (DM) is a chronic and potentially disabling disease which is reaching an epidemic proportion in many parts of the world. It is a major and growing threat to global public health. The biggest impact of the disease is on adults of working age; particularly in developing countries. The vast majority of cases of the diabetes fall into two broad categories: those having little or no endogenous insulin secretory capacity (IDDM or type 1 DM) and those who retain endogenous insulin secretory capacity but have a combination of resistance to insulin action and an inadequate compensatory insulin secretory response (NIDDM or Type 2 DM) (Fauci *et al*., 2012; American

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Diabetes Association, 2007). Centers for Disease Control and Prevention (CDC) report in 2011 estimated that nearly 26 million Americans have diabetes. (U.S. Department of Health and Human Services, 2011) Type 2 diabetes mellitus (DM) accounts for more than 90% of the diabetic population worldwide. Additionally, an estimated 79 million Americans have prediabetes. Rates of diabetes are increasing worldwide. The International Diabetes Federation predicts that the number of people living with diabetes will to rise from 366 million in 2011 to 552 million by 2030. (Neve *et al*., 2005) The top 10 countries in number of people with diabetes are currently India, China, the United States, Indonesia, Japan, Pakistan, Russia, Brazil, Italy, and Bangladesh. The prevalence of diabetes and its adverse health effects have risen more rapidly in South Asia than in any other region of the world. (Ghaffar *et al*., 2004) Thirty years ago, the prevalence of diabetes in India based on the Indian Council of Medical Research (ICMR) Multicentre survey (Tripathy and Chandalia, 2008) was around two percent in urban India and one percent in rural India. In just three decades, these prevalence rates have shot up to nine percent in urban India and three to eight percent in rural India, in adults over 20 years of age. These represents a 600 to 800% increase in prevalence rates of diabetes something which is unparallel in any Western nation. Indeed, India is now referred to as the "Diabetic Capital" of the world.

Further, Diabetes Mellitus is associated with several complications. The complications of diabetes mellitus include retinopathy, nephropathy, and neuropathy (both peripheral and autonomic). The risk for atherosclerotic vascular disease is also increased in persons with DM. The risk for microvascular and neuropathic complications is related to both duration of diabetes and the severity of hyperglycemia; the increased risk for vascular disease actually antedates the onset of hyperglycemia to the degree associated with diabetes mellitus (Fauci *et al*., 2012). Ferritin is the major iron storage protein and plays a key role in iron metabolism. Ferritin in the circulation is a secretory form of the protein which is glycosylated and differs in subunit composition from the storage form found in the cells. (Gibson and Macdonald, 1988) Serum ferritin concentration is directly related to body iron stores in healthy individuals, and is also an acute phase reactant which increases during inflammation. (Fumeron *et al*., 2006) Iron is a transition metal that can be easily become oxidized and thus acts as an oxidant.

The general effect of catalytic iron is to convert poorly reactive free radicals such as hydrogen peroxide into highly reactive radicals such as the hydroxyl radical. Increased accumulation of iron affects insulin synthesis and secretion from the pancreas, (Rahier *et al*., 1987) and interferes with the insulin extracting capacity of the liver (Niederau *et al*., 1984) and Iron deposition in muscle decreases glucose uptake because of muscle damage. (Merkel *et al*., 1988) Conversely, insulin stimulates cellular iron uptake through increased transferrin receptor externalization. (Davis *et al*., 1986) Iron deposition in the liver may also cause insulin resistance by interfering with the ability of insulin to suppress hepatic glucose production. (Kim *et al*., 2000) Reactive oxygen species interfere with insulin uptake through direct effect on insulin receptor function (Qian *et al*., 1988) and inhibiting the translocation of glucose transporter (GLUT4) in plasma membrane. (Bertelsen *et al*., 2001) Serum ferritin concentration is directly related to body iron stores in healthy individuals. In general population, body ferritin stores are positively associated with the development of glucose intolerance, type 2 diabetes mellitus. (Sultan *et al*., 2009)

This study intended to perform to find a link between serum ferritin and type 2 diabetes mellitus and also glycated hemoglobin as a blood glucose control marker in diabetic patients.

## MATERIALS AND METHODS

This study was conducted in the Department of Medicine, BLDE University's Shri B M Patil Medical College and Research Centre, Vijayapura from January 2014 to June 2015 on newly detected and known patients of type 2 diabetes mellitus. A total of 131 patients with type 2 diabetes mellitus were selected for the study. The patients fulfilling selection criteria were explained about the nature of the study. Those willing to participate were enrolled in the study after obtaining a written informed consent.

### Inclusion criteria

All the outpatients and inpatients of Shri B M Patil Medical College Hospital who are diagnosed or who are already known with type 2 Diabetes Mellitus.

### Exclusion criteria

- Chronic kidney disease.
- Chronic liver disease.
- Hypothyroidism.
- On Corticosteroid therapy.
- Severe anemia (Hb < 7 g %).
- Blood transfusion in last 3 months.

### Method of collection of data

Demographic data such as age, sex and occupation were recorded. Patients were interviewed and history regarding type 2 diabetes mellitus such as duration of disease, medication, personal history and history pertaining to the other co-morbid conditions was obtained. Further these patients were subjected to a thorough physical examination such as anthropometry (including height and weight), vitals (pulse rate, blood pressure and respiratory rate) and systemic examination. These findings were recorded and body mass index was calculated.

### Investigations

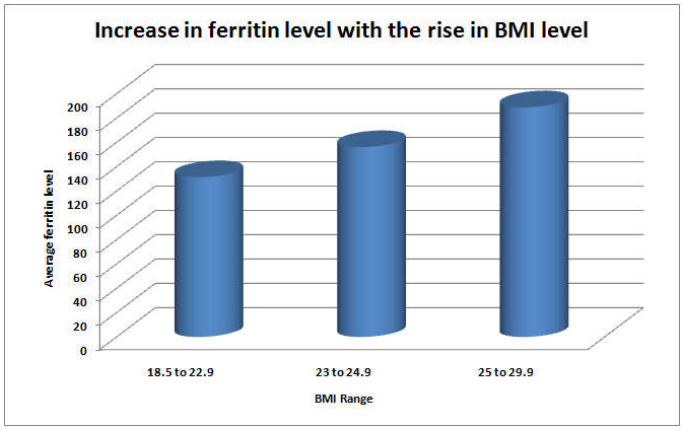
The selected patients underwent the following investigations.

- Complete blood count.
- Renal function test.
- Liver function test.
- Urine – Routine and microscopy.
- Blood sugar levels – Fasting and post prandial.
- Glycated hemoglobin (HbA1c)
- Fasting lipid profile
- Serum ferritin.

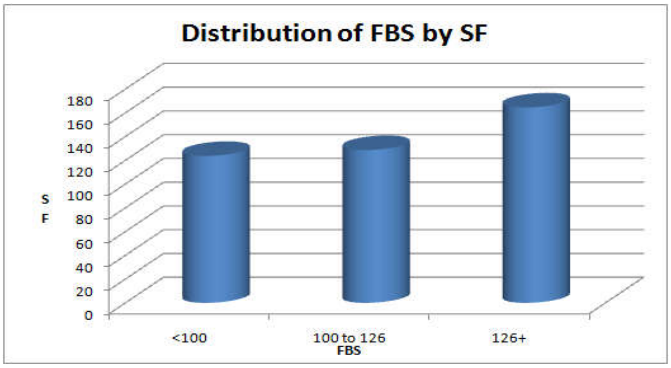
The data collected was analyzed using appropriate statistical methods using mean and standard deviation, Anova test, p-value and regression analysis.

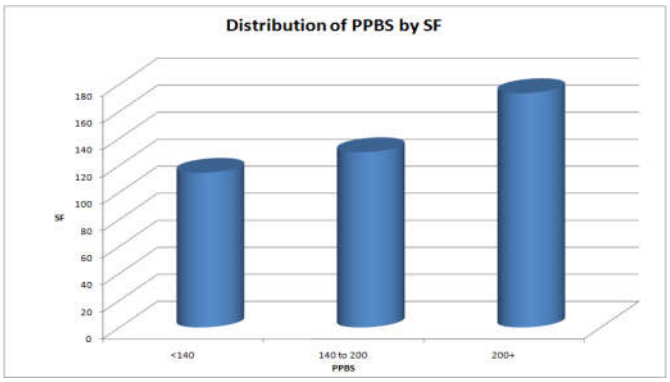
## RESULTS

A total of 131 patients were analyzed for the study. Patients age ranged from 30 to 90 years, maximum number of cases were in the age group of 50 to 60 that is 54 patients (41.2%), between 40 to 50 years 46 patients (35.1%) and between 60 to 70 years 19 patients (14.5%) and 70 to 80 years 7 patients (5.34%) in each group. The mean age of study population was 53.46 ± 10.74 years. Out of 131 patients 70 (53.43%) were males and 61 patients (46.56%) were females, accounting male to female ratio of 1.15:1. In the present study, we observed in 69.5% patients the duration of diabetes was 0 to 4 years. In 25.9 of patients the duration of diabetes was 5 to 9 years. In 3.8% of patients the duration of diabetes was 10 to 14 years. The mean duration of diabetes was 7.04 ± 3.25 years. We observed 105 patients (80.16%) were on oral hypoglycemic agents, 6 patients (4.58%) were newly detected and 20 patients (15.26%) were on combination of insulin and oral hypoglycemic agents. We observed in 47 patients (35.88%) BMI of 18.5 to 22.99, 42 patients (32.08%) had BMI of 25 to 29.99, 29 patients (22.14%) had BMI of 23 to 24.9 and 13 patients (9.92%) BMI was <18.5. The mean BMI was 23.95 ± 3.15 kg/m$^2$. We observed 90 patients (69%) had fasting blood glucose above 126mg/dl, 35 patients (27%) had 100 to 126mg/dl and 6 patients (4%) had normal fasting sugar levels. We observed 72 patients (55%) had postprandial blood glucose above 200mg/dl, 52 patients (40%) had 140 to 200mg/dl and 7 patients (5%) had normal postprandial sugar levels. In our present study 76 patients (58%) had HbAlc of more than 8.0%, 32 patients (24.4%) had HbAlc between 7.1 to 8.0% and 17 patients (12.9%) had HbA1C between 6.5 to 7.0%. The mean HbAlc level was 8.34± 0.84%. 79 patients (60%) had total cholesterol ≤ 200 mg/dl and remaining 52 patients (40%) had total cholesterol >200 mg/dl. LDL cholesterol was ≤ 100 mg/dl was observed in 64 patients (49%) and in 67 patients (51%), LDL cholesterol >100 mg/dl. In most of patients (53%) HDL cholesterol was >40 mg/dl, in 62 patients (47%) it was ≤40 mg/dl. In 92 patients (70.22%), triglycerides were ≤150 mg/dl, and in remainder 39 patients (29.77%) it was ≥150 mg/dl. Serum ferritin levels were in the range of 101 to 200ng/ml in 98 patients (74.7% of the cases). 18 patients had serum ferritin levels less than 100ng/ml and 15 patients had serum ferritin levels more than 200ng/ml. We found 47 patients whose BMI was in the range of 18.5 to 22.9 the mean serum ferritin was 131.4 ng/ml, 29 patients in the range of 23 to 24.9 mean ferritin was 156.2 ng/ml and 42 patients in the range of 25 to 29.9 the mean ferritin was 188.9ng/ml. We obtained a p-value of < 0.001 when we correlated serum ferritin levels with BMI. This p value was statistically significant.

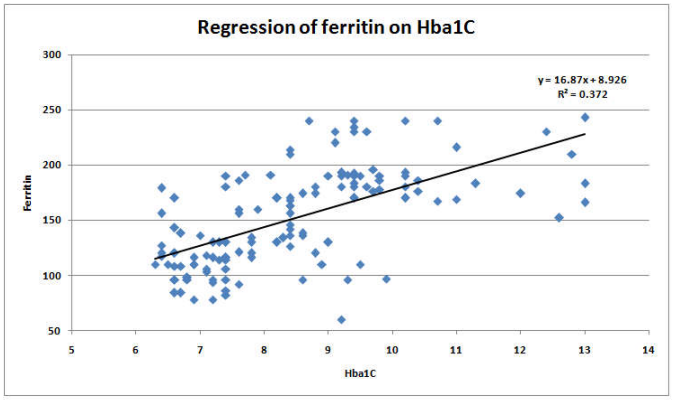



We found 90 patients whose FBS was >126mg/dl, the mean serum ferritin was 164.56 ng/ml, 35 patients in the range of 100 to 126mg/dl, the mean ferritin was 128.68ng/ml and 6 patients with FBS ≤100mg/dl, the mean ferritin was 123.75ng/ml. We obtained a p-value of ≤ 0.001, when we correlated serum ferritin levels with FBS. This p value is statistically significant. We also found 72 patients whose PPBS was >200mg/dl, the mean serum ferritin was 173.49ng/ml, 52 patients in the range of 140 to 200mg/dl, the mean ferritin was 129.77ng/ml and 6 patients with PPBS ≤140mg/dl, the mean ferritin was 114.53ng/ml. We obtained a p-value of ≤ 0.001 when we correlated serum ferritin levels with PPBS. This p value was statistically significant.




We found 76 patients whose HbAlc was >8%, the mean serum ferritin was 176.06ng/ml, 32 patients in the range of 7.1 to 8%, the mean ferritin was 124.71ng/ml, 17 patients in the range of 6.5 to 7%, the mean ferritin was 109.7 ng/ml and 6 patients with HbAlc ≤6.4%, the mean ferritin was 110ng/ml. We obtained a p-value of ≤ 0.001, when we correlated serum ferritin levels with HbAlc. This p value was statistically significant




**Correlation analysis:** A linear correlation between Hba1C and ferritin (r=0.6099)

## DISCUSSION

Management of type 2 diabetes mellitus is a challenge for health care workers, patients and their families. Current management standards focus on optimizing glycemic control to reduce the risks of long term complications. The main aim of our investigation was to clarify, whether there exists association between serum ferritin levels and glycated hemoglobin in patients of type 2 diabetes mellitus. In the present study of 131 patients with type 2 diabetes mellitus, we observed the levels of serum ferritin and compared it to various factors. In this cross sectional study, we found a linear association between serum ferritin levels and HbAlc. In the present study, there were 70 males & 61 females with mean Age distribution of 53.48+8.56. Majority of patients (41%) were in their sixth decade of life. In a study conducted by Raj *et al*. the mean age distribution among study population was 54.3+9.2 yrs, male and females were 57 and 29 respectively. In a study done by Bansal *et al*. (Pankaj *et al*., 2011) mean age of the patients was 45.70+1.6 years. In our study, the duration of diabetes varied from 0 to >15 yrs. We did not find any association between serum ferritin levels and duration of diabetes, but Kundu *et al*. (2013) found there is inverse correlation between serum ferritin and duration of diabetes. Some of our patients were on treatment either with oral hypoglycemic agents (80.15%), combination of oral hypoglycemic drugs and insulin (15.26%) and 4.58 % were newly detected diabetics. All of these patients when presented had either fasting blood sugar or post prandial blood sugar abnormality reflecting poor diabetic status. Most of our patients were having higher normal levels of serum ferritin. Same Conclusion was drawn by Raj S *et al*. [19] This issue needs further evaluation by comparing the diabetic patients with healthy non-diabetic individuals. In our study when levels of serum ferritin were compared with BMI, We found 47 patients whose BMI was in the range of 18.5 to 22.9 the mean serum ferritin was 131.4 ng/ml, 29 patients in the range of 23 to 24.9 the mean ferritin was 156.2 ng/ml and 42 patients in the range of 25 to 29.9 the mean ferritin was 188.9 ng/ml. This signifies there is a positive correlation between serum ferritin and BMI (p value <0.001). The same conclusion was drawn by Raj *et al*. (2013) and Sultan *et al*. (2009).

When correlated with HbA1c, the serum ferritin levels were definitely affected with HbA1c of 8% and above. There is direct correlation between serum ferritin and HbA1c levels, p-value being significant (p<0.0001). Similar observation was made by Raj *et al*. (2013) and Kundu *et al*. (2013). When serum ferritin levels were compared with fasting blood sugar, most of patients with fasting glucose abnormality had either higher or upper limit of normal serum ferritin levels (p<0.001; significant). In their study by Raj *et al*. (2013) (sample size 86 cases), observed elevated serum ferritin levels are associated with fasting glucose abnormality (p<0.01; significant). Similarly study done by Sultan *et al*. (2009) (sample size 40 patients) found a positive correlation of serum ferritin levels with fasting glucose abnormality (p<0.001; significant). Study by Mukesh *et al*. (2013) found higher levels of serum ferritin in patients with increasing fasting blood sugars. In our study, when levels of serum ferritin were compared with post prandial blood sugars, we found elevated serum ferritin levels with higher post prandial blood sugar levels (p<0.001), similar results observed by Mukesh *et al*. (2013). But study by Raj *et al*. (2013) found no correlation between serum ferritin and postprandial sugar levels. An attempt was made to correlate serum ferritin levels with fasting lipids. We found positive association between total cholesterol ($p < 0.1$, not significant), triglycerides ($p \leq 0.05$) and low density lipoprotein ($p < 0.001$) with serum ferritin levels, there was inverse relation between serum ferritin levels and high density lipoproteins (p value < 0.001). Study done by Raj *et al*. found no correlation between serum ferritin and total cholesterol, low density lipoproteins and serum triglycerides. But study done by Smotra *et al*. (2008) found significant relationship between increased serum ferritin and increased total cholesterol, triglyceride and decreased serum HDL levels. To overcome the bias with confounding factors and co-morbid conditions, may be large sample size is required. And also comparison of diabetic individuals with non-diabetic healthy individuals is essential to find out the true correlation of serum ferritin levels with other variables.

### Conclusion

There was positive association between serum ferritin and body mass index measurements. We found direct association between serum ferritin and fasting, postprandial blood sugars. We found positive association between serum ferritin levels and glycosylated hemoglobin as glycemic control. We also observed there was direct association between serum ferritin levels and fasting lipids (triglyceride and low density lipoproteins), but an inverse association with high density lipoproteins. When correlated with other variables like age, gender, duration of diabetes, total cholesterol, we found no significant correlation (p-value being statistically insignificant). Further studies to compare patients with type 2 diabetes mellitus and non- diabetic healthy individuals may be necessary to know the relationship serum ferritin levels with other variables.

### Limitations of the study

Overall, our findings suggest a potential beneficial role of serum ferritin in diabetes risk. Confirmation of these findings in future observational studies and specifically, well-designed randomized controlled trials potentially has significant public health implications given the high prevalence of higher serum ferritin status in the general population and the relative ease and low cost at which such an intervention may be implemented.

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