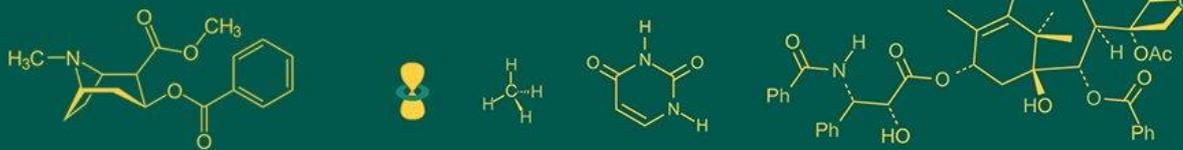


## International Journal of Advanced Biochemistry Research



ISSN Print: 2617-4693

ISSN Online: 2617-4707

IJABR 2020; 4(1): 16-19

[www.biochemjournal.com](http://www.biochemjournal.com)

Received: 10-11-2019

Accepted: 12-12-2019

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## Study of iron markers and their relationship with HbA1c level in type 2-DM-Bagalkot tertiary care centre

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**Abstract**

Diabetes Mellitus (DM) is one of the most prevalent endocrine disorders in the world. It comprises a group of common metabolic disorders that share common phenotype of hyperglycemia. Impaired insulin release in Type 2DM is linked to various trace elements like iron, magnesium, chromium etc. Systemic iron overload leads to increased oxidative stress which results in abnormal glucose metabolism. The defects in insulin-producing and insulin-sensitive tissues caused by iron-dependent catalysis is via the Fenton's reaction of reactive oxygen radical species.

Present study was undertaken to assess level of serum ferritin, free iron concentration, TIBC, transferrin saturation in type 2 Diabetes mellitus patients with good and poor glycaemic control and find out correlation between serum ferritin, free iron concentrations with glycaemic control. The study was conducted between January-August 2018 at SNMC & HSK Hospital Bagalkot. It's a case control study. Sample size included 120 subjects out of which 60 are diagnosed Type 2DM (cases) attending medicine OPD at SNMC & HSK, RC Bagalkot and 60 Healthy control appropriately matched for age and sex. The glucose parameters and serum iron, ferritin, TIBC, Transferrin saturation and Hb were high in cases compared to controls and was statistically significant. Serum iron and ferritin showed positive correlation with impaired glycaemic control. From this study it suggests that vital role of iron is metabolically deranged in diabetic patients.

**Keywords:** Diabetes mellitus, iron, ferritin, TIBC, transferrin, Hb, HCT

**1. Introduction**

Diabetes Mellitus (DM) is one of the most prevalent endocrine disorders in the world. Impaired insulin release and glycosylation of hemoglobin in Type 2DM is linked to release of various trace elements like iron, magnesium, chromium etc. The macronutrients like fat and carbohydrate which have an impact on Type 2 Diabetes is understood, but role of many micronutrients is not well established<sup>[1]</sup>. Minerals in addition to being structural components of body tissues are also involved in various physiological processes, such as proper metabolism and energy production. They also play a clear role in the synthesis, storage and secretion of insulin as well as its conformational integrity. According to some scientists, systemic iron overload contribute to abnormal glucose metabolism leading to T2DM by insulin deficiency as a result of oxidative stress on pancreatic beta cells leading to cell death and decrease insulin secretion or insulin resistance caused directly by iron overload and hepatic dysfunction<sup>[2]</sup>.

Iron is a potential catalyst involving cellular reactions which produces Reactive Oxygen Species. These Reactive Oxygen Species induces oxidative stress and damage to tissues which triggers the risk for Type 2 diabetes<sup>[3]</sup>. This oxidative stress on pancreatic beta cells leads to cell death resulting in decrease insulin secretion or insulin resistance.<sup>4</sup> As a result there is decrease in uptake of iron resulting in increased circulatory pool of catalytic iron. Increase blood glucose in diabetes mellitus also stimulates non enzymatic glycosylation of several proteins including hemoglobin. Glycosylation of hemoglobin also leads to increase in iron release from protein<sup>5</sup>. The defects in insulin-producing and insulin-sensitive tissues caused by iron-dependent catalysis is via the Fenton's reaction of reactive oxygen radical species which impair insulin signaling in skeletal muscle and liver<sup>[6]</sup>.

The study of individual susceptibility and of the mechanism that influences tissue iron and damage are proposed to be valuable in anticipating and treating diabetic complications.

There is considerable interest in understanding the relationship between insulin and iron pool in Diabetes mellitus. However it is unclear, whether elevated iron confers an increased risk of diabetes mellitus in the general population. Variable findings have been obtained for iron profile status from different studies. Therefore in the present study it has been intended to determine the status of parameters related to iron metabolism in type 2 diabetes mellitus patients.

**2. Objectives**

1. To study and compare the levels of Serum Ferritin, Iron, Total Iron Binding Capacity (TIBC), Transferrin saturation, Hemoglobin (Hb), Hematocrit (HCT) and HbA1c in Type-2DM and controls.
2. To correlate these iron parameters with HbA1c in Type 2-DM.

**3. Material & Methods**

The study was conducted between January-August 2018 at SNMC & HSK Hospital Bagalkot. Informed written consent was taken both from patients and controls. Ethical clearance was obtained from institutional ethics committee. Sample size included 120 subjects out of which 60 are diagnosed Type 2DM (cases) attending medicine OPD at SNMC & HSK, RC Bagalkot and 60 Healthy control appropriately

matched for age and sex. Age group between 35-65yrs was included both for cases and controls.

**Inclusion criteria:** Diagnosed Type 2DM with FBS > 126mg/dl, PPBS >200mg/dl and HbA1c >7%, with duration of diabetes for 5yrs.

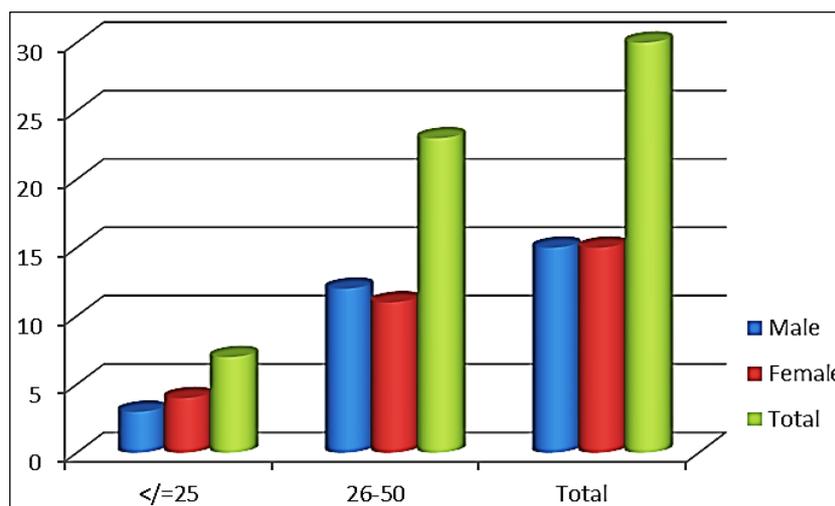
**3.1 Exclusion criteria:** Anemia, chronic kidney disease, chronic liver disease, hypertension, recent blood transfusion, pregnancy, drug history, Diabetes mellitus with complications.

After overnight fasting for 8-12hrs about 5ml of venous blood was drawn with aseptic precautions. 3ml in plain vials for glucose, ferritin iron, TIBC estimation and 2ml in EDTA vials for HbA1c, Hb & HCT.

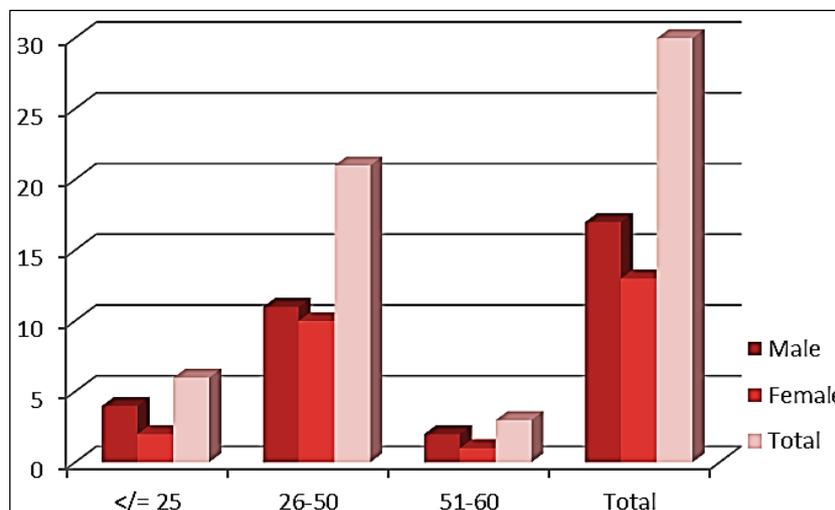
- **Sample size:** According to A. Manikundan *et al.*, [7] Ferritin levels were considered for sample size calculation. Sample size of cases and controls were 28. Total sample size = 56.
- Student ‘t’ test, Pearson’s Correlation tests were applied, with p <0.05 as significant.

**4. Results**

In the present study, there were 60 cases with Type 2Diabetes mellitus and 60 controls appropriately mathd for age and sex.



**Fig 1:** Age and sex distribution of controls



**Fig 2:** Age and sex distribution of cases

**Table 1:** Serum glucose level & iron parameters in cases and controls.

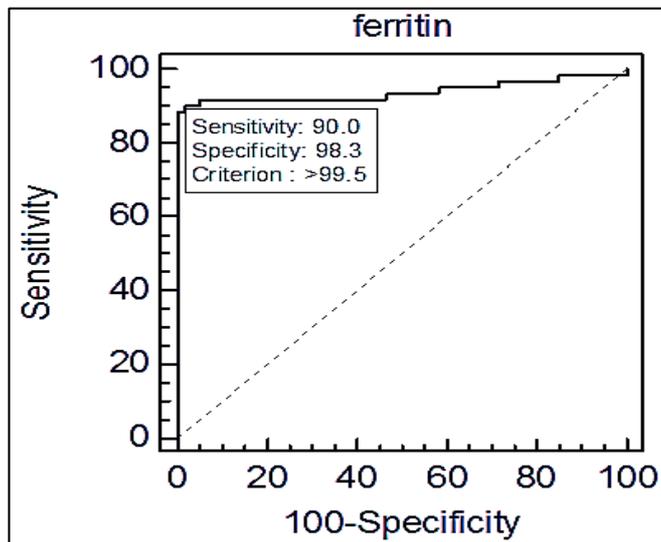
Parameters	Cases	Controls	'p'
FBS(mg/dl)	225.6±67.7	86.3±9.8	0.000***
PPBS(mg/dl)	300.6±45.8	136.4±12.6	0.000***
HbA1c (%)	9.3±2.1	5.4±0.7	0.000***
Ferritin (ng/ml)	291.4±145.0	62.9±16.4	0.000***
Iron (µg/dl)	168.6±122.2	60.2±8.3	0.000***
TIBC (µg/dl)	209.8±72.3	383.0±118.5	0.000***
Transferrin saturation (%)	42.8±23.0	30.6±10.7	0.000***
Hb (gm/dl)	12.7±1.9	11.7±1.3	0.002***
HCT (%)	37.6±5.8	34.5±4.3	0.001***

\*\*\* p<0.05-highly significant.

**Table 2:** Correlation between iron parameters and HbA1c in cases

Iron Parameters	'r'	'p'
Ferritin (ng/ml)	0.48	0.000***
Iron(µg/dl)	0.50	0.000***
Transferrin saturation (%)	0.29	0.001***
Hb(gm/dl)	0.30	0.001***
HCT (%)	0.33	0.000***
TIBC (µg/dl)	-0.59	0.000***

p<0.05- highly significant.



Area under ROC curve (AUC) = 0.939.

Significance level 'p' (area = 0.5) <0.0001\*\*\*

**Fig 3:** Receivers operating characteristic curve for serum ferritin in Type 2DM patients.

**5. Discussion**

Type II Diabetes results from the interaction of a genetic predisposition, diet and environmental risk factor. Diabetes Mellitus is a metabolic disorder with increased level of plasma glucose, relative deficiency of insulin secretion or with insulin resistance at the tissue level. Compared to people with Type 2 DM who have substantial insulin resistance, people with Type 1 DM range from normal weight or underweight with predominant deficiency of insulin secretion<sup>[8]</sup>. Scientific evidence suggests, there are unsuspected influences between metabolism of iron status and type 2 diabetes. Since iron affects metabolism of glucose and glucose metabolism, and this impinges on several iron metabolic pathways. The relationship between them is bidirectional. These relationships are influenced by oxidative stress and inflammatory cytokines which amplifies and potentiates the initiated events<sup>[9]</sup>. A significant impact of tissue iron excess on systemic effects of diabetes mellitus

is suggested by recent research studies in which iron appears to influence the development of multiorgan dysfunctions in T2DM. Hyperglycemia in T2DM may also change the osmolarity of blood which may be one of the factors for increased blood iron which also increased transferrin saturation due to hemolysis or fragility of RBC<sup>[8]</sup>.

In the present study glucose parameters and among iron indices iron, ferritin, TIBC, Transferrin saturation and Hb were high in cases compared to controls and was statistically significant whereas haematocrit was lower in cases compared to controls and statistically significant.

According to our findings elevated transferrin saturation indicates ineffective erythropoiesis, iron accumulation in human tissues which may have impaired the insulin action. This condition may lead to mild iron overload in type 2 diabetes mellitus patients. In the general population, body iron stores are positively associated with the development of glucose intolerance and finally type 2 diabetes mellitus<sup>[10]</sup>. Thomas MC *et al.*, in 2003 have shown that the prevalence of elevated transferrin saturation (>35%) was 3-4-fold higher in patients with diabetes mellitus, compared with historical prevalence in the general population. Independent associations with elevated transferrin saturation were found in male and increased fasting plasma glucose (all P<0.0001). Patients with elevated transferrin saturation were younger, but had a similar duration of diabetes mellitus, possibly suggesting an earlier age of onset. These studies have shown the elevated transferrin saturation in T2DM patients with earlier age of onset which is also consistent with our findings<sup>[11]</sup>.

Acton RT *et al.*, in 2006 have shown that the transferrin saturation in men of different races (White, Black, Hispanic and Asian having transferrin saturation 39%, 41%, 38% and 33% respectively) and women of different races (White, Black, and Asian having transferrin saturation 34%, 36%, 30% respectively) having diabetes mellitus<sup>[12]</sup>.

In study done by Salonen *et al*, serum ferritin had significant positive correlation with plasma glucose, serum triglyceride and serum apolipoprotein B concentration and inversely correlated to serum HDL2 cholesterol levels, all of which are components of insulin resistant syndrome<sup>[13]</sup>. Which was in accordance to our study. In a study by Nan Hee Kim *et al*, the serum ferritin had a positive correlation with fasting plasma glucose, BMI, and fasting C Peptide level, an indicator of Hyperinsulinemia<sup>[14]</sup>.

Hemoglobin, Iron, TIBC and Ferritin values are found to be positively correlated with HbA1c in DM group. Serum Ferritin is a marker of insulin resistance. It is an independent determinant of poor metabolic control in diabetic patients. Positive correlation between FBS and HbA1c as well as free iron and HbA1c, indicates hyperglycemia causing increased glycation of hemoglobin and increased release of free iron from glycated proteins like hemoglobin. This makes a vicious cycle of hyperglycemia, glycation of hemoglobin and increase in levels of free iron. This increased presence of free iron pool will enhance oxidant generation leading damage to biomolecules and lead to complications.

**6. Conclusion**

This study shows the elevated levels of serum iron and ferritin in Type 2 Diabetes mellitus patients with poor glycaemic control. Serum iron and ferritin showed positive correlation with impaired glycaemic control. These suggest important role of iron in metabolic derangement in diabetic

patients and its complications. It suggests that vital role of iron is metabolically deranged in diabetic patients.

### 7. Limitation

Further a large case control studies and studies at the molecular level are required to know the role of serum free iron concentration in modifying the effect of insulin and oxidative stress in diabetes mellitus.

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