

Role of Iron Metabolic Indices in Type 2 Diabetes Mellitus

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Abstract

Introduction:Type 2 Diabetes Mellitus is a major growing health issue worldwide. Role of micro nutrients is not well established. Serum Ferritin, an acute phase reactant is a marker of iron stores in the body. Iron overload is increasingly being connected to insulin resistance in type 2 Diabetes Mellitus Patients.

Aims & Objectives:1)Study of levels of Serum Iron, Total Iron Binding Capacity (TIBC), Ferritin in Type 2 Diabetes Patients to find any statistically significant relationship between Iron status and Diabetes mellitus.2)To find association of elevated Serum Ferritin level with Diabetes mellitus & its Correlation with Glycated Hemoglobin (HbA1C).

Materials & Methods: The Study Population consist of 120 individuals. Out of them 60 were type 2 Diabetes Patients(Cases) and 60 were normal healthy individuals (Controls). Comparison of Serum Iron, TIBC, Ferritin, FBS, PPBS and HbA1C was done between cases & Controls. Correlation of Serum Ferritin with HbA1C in test group was seen.

Results:We found that FBS($P<0.05$), PPBS($P<0.05$), HbA1C($P<0.05$) and Serum Ferritin ($P<0.05$) of case group were significantly higher than that of Control group. Statistically highly significant Positive Correlation is observed between Ferritin & HbA1C levels in Type 2 Diabetes with ($r =0.6083$) and ($P=0.001$).We also observed that there was no increase in serum Iron among those with DM.

Conclusion: We can Conclude that Serum Ferritin can be considered as sensitive marker of Iron status in Diabetic group. Excess tissue Iron will increase the production of free radicals which in turn amplifies the steps involved in inflammatory lesion. Serum Iron, TIBC & Ferritin may be monitored at regular intervals in those with Diabetes mellitus so that appropriate measures can be taken.

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I. Introduction

Diabetes mellitus is one of the most common diseases of current era which is characterized by hyperglycemia either due to insulin deficiency or insulin resistance. DM type 2 is also leading cause of coronary artery disease, peripheral artery disease, end-stage renal disease (ESRD) and adult blindness. With an increasing incidence worldwide, DM will be a leading cause of mortality and morbidity [1].Elevated iron stores may induce 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 [2-11]. Raised Serum Ferritin may possibly be related to the occurrence of long term complications of diabetes, both micro vascular and macro vascular [12-13].The level of glycated hemoglobin (HbA1c) reflects the mean blood glucose concentration over the preceding 6–8 weeks. Measurement of HbA1c therefore provides valuable information for management of diabetes mellitus[14] but HbA1c may be affected by a variety of genetic, haematologic and illness-related factors [15] like haemoglobinopathies (depending on the assay employed), certain types of anemia, and disorders associated with accelerated red cell turnover such as malaria [14,16] so it is important to have some useful alternative. Overall there is paucity of literature especially from India showing direct evidence of relation between Diabetes Mellitus and iron overload, this research was designed to enlighten this path and to find association of elevated serum ferritin level with Diabetes mellitus type 2 and its correlation with level of glycated hemoglobin .Type 2 Diabetes is diagnosed by elevation of Plasma Glucose greater than126 mg/dl in fasting state and greater than 200 mg/dl in 2hrs after 75gm of glucose load. Diabetic complications include retinopathy, neuropathy, IHD and stroke (17). In the prevention of Type 2 Diabetes, diet and lifestyle plays a major role. The macronutrients like fat and carbohydrate have an impact on Type 2 Diabetes. Role of many micronutrients is not well established. Studies suggest that magnesium, chromium, calcium and iron may have a role in Insulin Resistance or Diabetes. Iron, a potential catalyst involves in cellular reactions which produces Reactive Oxygen Species. These Reactive Oxygen Species induces oxidative stress and damage to tissues which alters the risk for Type 2 diabetes (18).

II. Aims & Objectives

1. To Study levels of Serum Iron, Total Iron Binding Capacity (TIBC), Ferritin in Type 2 Diabetes Patients to find any statistically significant relationship between Iron status and Diabetes mellitus.
2. To find association of elevated Serum Ferritin level with Diabetes mellitus & its Correlation with Glycated Hemoglobin(HbA1C).

III. Material and Methods:

3.1 Study design:-This was a case control study conducted at a tertiary care institute of NRI Medical college & General Hospital for duration of six months. The Study included 120 subjects out of which 60 were cases and 60 were controls.

3.2 Inclusion criteria:

- 1)**Cases:** Diagnosed Type 2 diabetes mellitus patients on treatment, in the age group of 40-65 years.
- 2)**Controls:** This group consisted of age and sex matched healthy subjects (Non diabetic) coming to the hospital as patient's attendant and also from medical or paramedical staff, persons attending OPD for routine checkup aged between 40-65 years

3.3 Exclusion criteria:

- 1) Type 1 Diabetes mellitus
- 2) Other states associated with altered serum ferritin levels like:
 1. Hemochromatosis
 2. Chronic alcoholics
 3. Overt thyroid dysfunction
 4. Chronic kidney disease
 5. Chronic liver disease
 6. Corticosteroid therapy
 7. Chronic inflammatory conditions like SLE/ rheumatoid arthritis

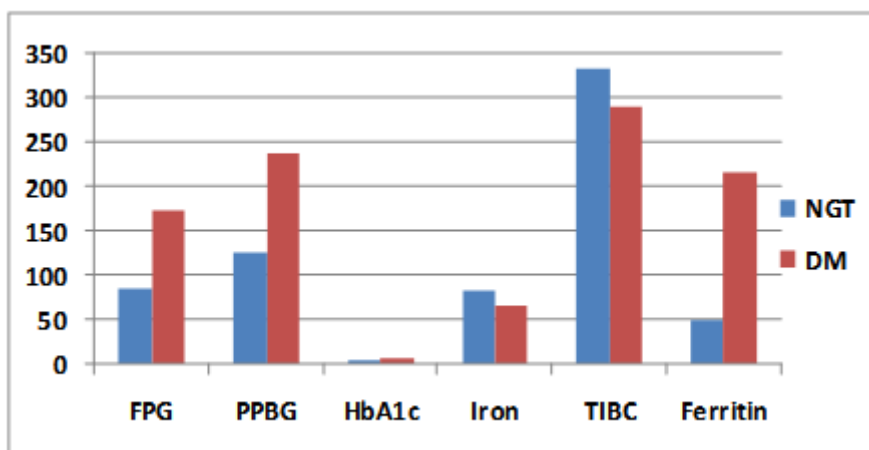
Sampling and Data collection:-Each patient's written informed consent was taken to participate in the study. The following investigations were carried out on the study subjects like Serum Iron, TIBC, Ferritin, FPG, PPPG and HbA1C. Blood samples were collected after 12 hrs fasting in the vacutainers for estimation of FPG. Post prandial (PPPG)sample was also taken. Plain vacutainer for serum iron, TIBC, Ferritin and EDTA vacutainer for HbA1C and for plasma glucose sodium fluoride vacutainers were used. The samples were separated by centrifugation at 2400 rpm. Glucose was analyzed in DADE Dimension automated system. Ferritin was estimated by Automated Electro Chemiluminescence(ECLIA) method using commercially available kit by ROCHE Cobas e411 and Iron & TIBC were estimated by RANDOX Imola. HbA1c was tested by BIO RAD D10 system which is based on the principle of High Performance Liquid Chromatography (HPLC).

IV. Results

Data evaluation was done using SPSS programme. The results were expressed as Mean (standard deviation). The P value was used to compare the different groups. The P value <0.05 was considered significant. The mean and standard deviation of biochemical characteristics of the two groups were calculated. The biochemical parameters include Fasting Plasma Glucose (FPG), Post prandial Plasma Glucose (PPPG), HbA1C Iron, TIBC and Ferritin.

Table:1 Comparison of biochemical parameters for NGT(controls) and DM(test) group

Parameter	NGT (n-60)	DM (n-60)	P value
FPG (mg/dl)	85.72 (8.22)	174.47(54.78)	<0.05
PPPG (mg/dl)	127.23 (12.31)	237.63 (66.6)	<0.05
HbA1c (%)	5.31 (0.38)	7.71 (1.56)	<0.05
Iron (µg/dl)	83.98 (22.89)	67.38 (39.57)	<0.05
TIBC (µg/dl)	332.48 (65.89)	291.61 (65.86)	<0.05
Ferritin (ng/ml)	51.07 (35.54)	216.09 (119.02)	<0.05

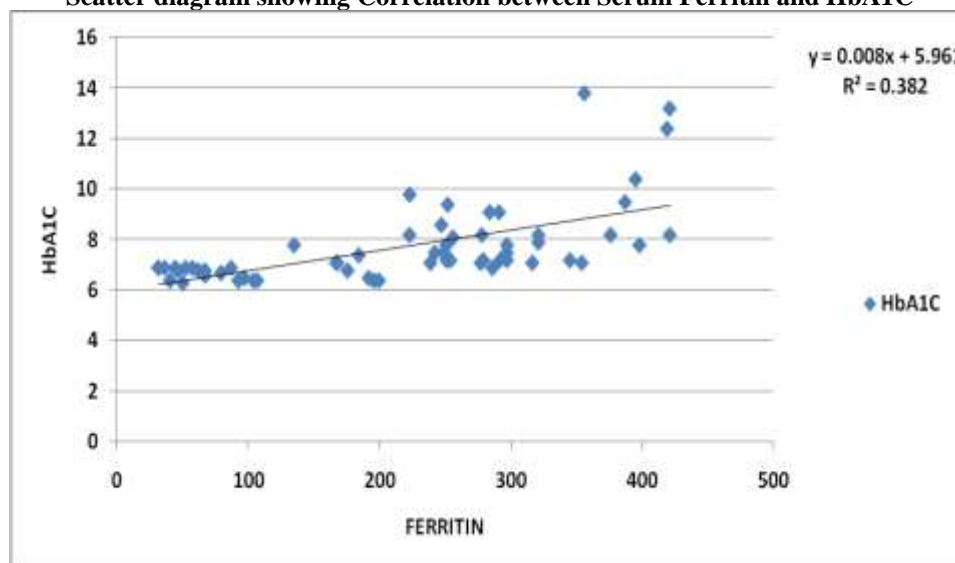


Correlation between serum ferritin and HbA1c was also assessed. The mean HbA1c of case group was 7.71%. The correlation between glycated haemoglobin and serum ferritin was done by Pearson correlation test and it showed a significantly positive correlation ($r=0.6083$) with serum ferritin [mean= 216.09 ± 119.02 ng/mL].

Table 2: Correlation between serum ferritin and HbA1c levels

Group	N	Mean	Std. Deviation	Pearson Correlation	P-Value
S. Ferritin	60	216.09	119.02	0.6083	0.001
HbA1C	60	7.71	1.56		

Scatter diagram showing Correlation between Serum Ferritin and HbA1C



V. 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 [19]. In diabetic subjects, a positive correlation between increased serum ferritin and poor glycemic control, reflected by higher HbA1c, has been suggested by Eschwege et al [20]. 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 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 [21]. Recent studies shows increase in iron stores (Ferritin) predicts the risk of developing type 2 diabetes, while decrease in iron level is protective. Damage caused by iron also triggers the events of chronic diabetes

complication, in coronary artery responses and endothelial dysfunction [21]. Tissue iron excess will increase the production of free radicals which in turn amplifies the steps involved in inflammatory lesion [22].

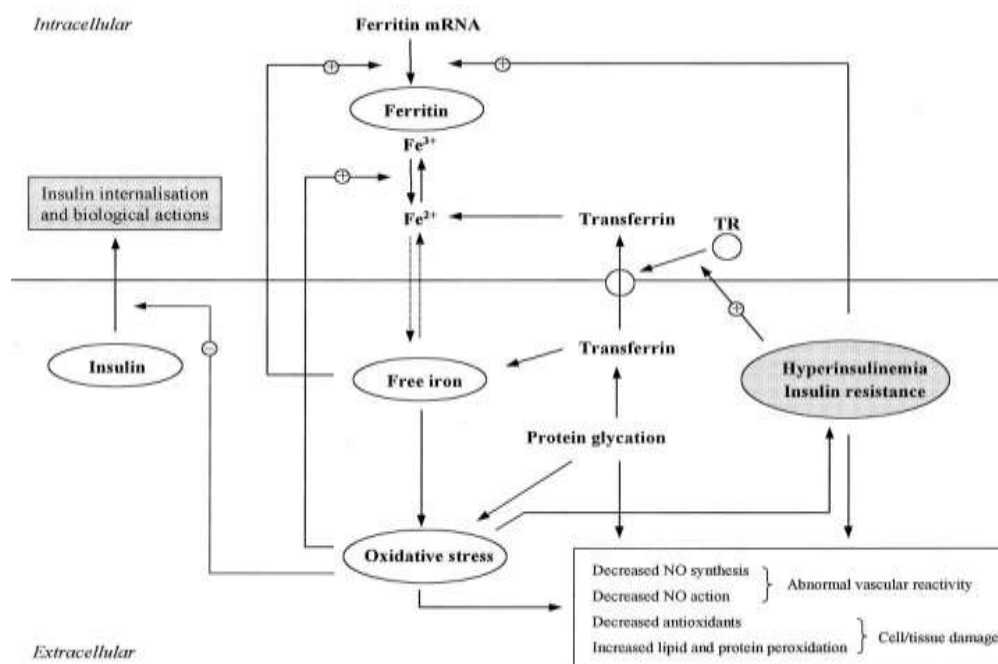


FIG. 1. Schematic representation of iron interactions with insulin resistance and oxidative stress. Insulin influences iron metabolism.

Stimulates ferritin synthesis and facilitates iron uptake by the cell through the translocation of transferrin receptors from the intracellular compartment to the cell surface. Conversely, iron influences glucose metabolism. Iron is a potent prooxidant that increases the cell oxidative stress, causing inhibition of insulin internalization and actions, results in hyperinsulinemia and insulin resistance. Free iron also exerts a positive feedback on ferritin synthesis, while oxidative stress increases the release of iron from ferritin. The increased oxidative stress and insulin resistance cause endothelial and tissue damage. Protein glycation, as seen in diabetes, further amplifies these abnormalities stimulating iron release from transferrin, increasing the cell oxidative stress and directly causing endothelial and tissue damage. NO, nitric oxide; TR, transferrin receptor; (—), stimulation; (—), inhibition; dotted lines, possible trafficking or iron through the cell membrane. Ferritin values are found to be positively correlated in the male and female subjects when NGT group is compared against DM group. Serum Ferritin is a marker of insulin resistance. It is an independent determinant of poor metabolic control in diabetic patients. Diabetic microangiopathy is associated with abnormal increased ferritin level in serum. Men with moderately higher ferritin levels had a significantly worse coronary risk profile than men with lower levels. Mean serum ferritin levels are higher in men than in premenopausal women [23].

In study done by Salonen et al, serum ferritin had significant positive correlation with plasma glucose [24]. In a study by Nan Hee Kim et al, the serum ferritin had a positive correlation with fasting plasma glucose [25]. In our study there was no increase in serum Iron among those with DM. The low levels of serum iron in female group than the male group may be due to the reason that they are mostly anemic due to physiological process like menstruation and pregnancy leading to iron deficient state. Increase in Serum Iron level contribute to macro vascular disease as iron has an adverse effect on endothelium and accelerates the development of atherosclerosis [26]. During the course of atherosclerotic plaque formation, ferritin gene expression increases [27]. In our study we observed there was no increase in serum iron among those with diabetes mellitus. Even though there is no increase in serum iron in diabetes, iron participates in the formation of free radicals which are highly toxic and capable of inducing lipid peroxidation. Invariably in iron overload, insulin resistance is reported. Hence periodic monitoring of serum iron may be needed among those with diabetes mellitus. Further long term prospective studies including all the parameters of iron metabolism may throw more information in this field.

VI. Conclusion

We can Conclude that Serum Ferritin can be considered as sensitive marker of Iron status in Diabetic group. Excess tissue Iron will increase the production of free radicals which in turn amplifies the steps involved in inflammatory lesion. Serum Iron, TIBC & Ferritin may be monitored at regular intervals in those with Diabetes mellitus so that appropriate measures can be taken.

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