Serum ferritin level in patients with type-2 diabetes mellitus

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Abstract
Aim: To measure the level of Serum Ferritin, Fasting and Postprandial Blood Sugar & Lipid Profiles in patient with Type-2 Diabetes Mellitus with and without cardiovascular involvement.

Material and methods: 50 patients of Type-2 Diabetes Mellitus (DM) without any cardiovascular involvement, 50 patients of Type-2 Diabetes Mellitus with cardiovascular involvement and 50 age and sex matched normal healthy control were studied. Blood samples were analyzed for ferritin estimation, Fasting Blood Sugar (FBS), Post Prandial Blood Sugar (PPBS), HbA1c and lipid profile.

Results: Ferritin levels are significantly high in patients of DM with Cardio Vascular Disease (CVD) (368 ± 67 ng/ml) than DM without Cardio Vascular Disease (192 ± 32 ng/ml) and controls (65 ± 14 ng/ml). There is statistically significant difference in ferritin levels in patients of DM with CVD (368 ± 67 ng/ml) than DM without CVD (192 ± 32 ng/ml).

Conclusion: Serum ferritin is an important and independent predictor of the development of diabetes mellitus and its cardiovascular complications.

Keywords: Type-2 Diabetes Mellitus, CVD, Ferritin

1. Introduction
Diabetes mellitus (DM) is a group of common metabolic disorders that share the phenotype of hyperglycemia. It is caused by a complex interaction of genetics and environmental factors.1

Type 2 Diabetes mellitus is characterized by impaired insulin secretion, insulin resistance, excessive hepatic glucose production, and abnormal fat metabolism. Obesity, particularly visceral or central (as evidenced by the hip-waist ratio), is very common in type 2 DM (80% or more are obese). In the early stages of the disorder, glucose tolerance remains near-normal, despite insulin resistance, because the pancreatic beta cells compensate by increasing insulin output. As islets in certain individuals are unable to sustain the hyperinsulinemic state. Impaired Glucose Tolerance (IGT), characterized by elevations in postprandial glucose, then develops. A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycemia. Eventually, beta cell failure ensues.2

The regulation of blood-iron levels is mediated by the protein ferritin. Ferritin can release iron if the blood has a low iron concentration, and it can help to store excess iron if the blood and tissues have a high iron concentration. Hence, ferritin functions as a "buffer" against iron deficiency and iron overload. 2

Ferritin has the shape of a hollow sphere. Inside the sphere, iron is stored in the Fe(III) oxidation state. It is incorporated in the mineral ferrhydrite, [Fe(OH)3]·H2O, which is attached to the inner wall of the sphere. To release iron when the body needs it, the iron must be changed from the Fe(III) to the Fe(II) oxidation state. Then, the iron leaves through channels in the spherical structure.2

Although the exact mechanism of iron-induced diabetes is uncertain, it is likely to be mediated by three key mechanisms: 1) insulin deficiency, 2) insulin resistance, and 3) hepatic dysfunction. An understanding of the pathogenic pathways of iron-induced diabetes is derived mainly from studies on animal models of hemochromatosis.3

Present study was carried out to study the level of Serum Ferritin, Fasting and Postprandial Blood Sugar & Lipid Profiles in patient with Type-2 Diabetes Mellitus with and without cardiovascular involvement to determine its association in development of insulin resistance and also its relation to diabetes complications.

2. Material and Methods
2.1 Study Design
The study was carried out at Clinical Chemistry Laboratory, Shree Sayajirao General Hospital and Medical College, Vadodara, from July 2013 to November 2013 after obtaining Ethical Clearance from the Institutional Ethics Committee for Human Research, Medical College and S.S.G. Hospital, Baroda. The study parameters were analyzed on Fully Automated Biochemistry Analyzer.

After taking informed consent blood samples were collected in fluoride vacutainer for Fasting Blood Sugar and Post Prandial Blood Sugar (PPBS), in plain vacutainer for biochemical parameters like Lipid profile and in EDTA vacutainer for HbA1c. Samples for PPBS were collected after 2 hours of taking a meal.

2.2 Inclusion Criteria
1. Patients on hypoglycemic drugs or insulin for Type 2 DM for 6 months to 2 years were included in study groups.
2. Patients of Type 2 DM who were clinically diagnosed Ischemic Heart Disease (by ECG changes and other cardiac markers) included in study group.

2.3 Exclusion Criteria
Subjects who have recently received blood transfusion or donated blood, with active infections, having haemoglobinopathies or bleeding disorder excluded from study.
The subjects selected for the study were grouped as follows: 

**Group I** – Control group: This group consisted of age and sex matched healthy subjects coming to the hospital for fitness purpose and also from medical or paramedical staff, persons attending OPD for routine checkups and fitness certificate. (n=50),

**Group II** – Type-2 Diabetes Mellitus patients without any cardiovascular involvement. (n=50) and

**Group III** – Type-2 Diabetes Mellitus patients with cardiovascular involvement. (n=50)

Serum ferritin estimation was done by solid phase direct sandwich ELISA method using DIA. Metra S.R.L. ELISA kit on Microplate reader Bio-Rad 680.

Calibration graph was prepared using reference standard set of 0, 5, 20, 100, 400, and 1,000 ng/mL and results were calculated accordingly.

Serum lipid profile (Cholesterol by CHOD-PAP method, LDL & HDL by Direct Enzymatic Colorimetric method, VLDL by Calculation), serum Urea (GLDH fixed time method), serum creatinine (Jaffe’s method), HbA1c (Immunoturbidimetric method) and plasma glucose (GOD-POD method) were measured by fully automated biochemistry analyzer Miura-300.

### 2.4 Statistical Method

Data analysis was done by MedCalc Version 11.5.0.0.

Statistical analysis was done by using t-test to find out significance of difference between two groups and correlation coefficient to find out statistical correlation between two variables and its significance. Interpretation was done according to p-value as follows:

- p < 0.05 was considered significant
- p ≥ 0.05 was considered not significant

### 3. Results

As defined in materials and methods, the study group consisted of 150 subjects with 50 subjects in each group;

#### Table 1: Comparison of FBS, PP2BS, HbA1c, Ferritin and Lipid Profiles in Controls (Group I) and DM without CVD (Group II)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (Group I)</th>
<th>DM without CVD (Group II)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS (mg/dl)</td>
<td>99 ± 14</td>
<td>127 ± 26</td>
<td>p&lt; 0.05</td>
</tr>
<tr>
<td>PP2BS (mg/dl)</td>
<td>120 ± 18</td>
<td>193 ± 66</td>
<td>p&lt; 0.05</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.6 ± 0.6</td>
<td>7.8 ± 1.6</td>
<td>p&lt; 0.05</td>
</tr>
<tr>
<td>Serum Ferritin (ng/ml)</td>
<td>65 ± 14</td>
<td>192 ± 32</td>
<td>p&lt; 0.05</td>
</tr>
<tr>
<td>Serum Total Cholesterol (mg/dl)</td>
<td>186 ± 28</td>
<td>232 ± 40</td>
<td>p&lt; 0.05</td>
</tr>
<tr>
<td>Serum HDL Cholesterol (mg/dl)</td>
<td>35 ± 0.6</td>
<td>44 ± 7</td>
<td>p&lt; 0.05</td>
</tr>
<tr>
<td>Serum LDL Cholesterol (mg/dl)</td>
<td>131 ± 23</td>
<td>145 ± 32</td>
<td>p&lt; 0.05</td>
</tr>
<tr>
<td>Serum VLDL Cholesterol (mg/dl)</td>
<td>20 ± 9.3</td>
<td>43 ± 17</td>
<td>p&lt; 0.05</td>
</tr>
<tr>
<td>Serum Triglyceride (mg/dl)</td>
<td>130 ± 54</td>
<td>124 ± 32</td>
<td>p&gt; 0.05</td>
</tr>
</tbody>
</table>

This table shows that FBS, PP2BS, HbA1c, Ferritin, Serum Total Cholesterol, HDL and VLDL is significantly high in patients of DM without CVD (Group II) than controls (Group I) (p<0.05).

#### Table 2: Comparison of FBS, PP2BS, HbA1c, Ferritin and Lipid Profiles in DM without CVD (Group II) and DM with CVD (Group III)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DM without CVD (Group II)</th>
<th>DM with CVD (Group III)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS (mg/dl)</td>
<td>127 ± 26</td>
<td>234 ± 72</td>
<td>p&lt; 0.05</td>
</tr>
<tr>
<td>PP2BS (mg/dl)</td>
<td>193 ± 66</td>
<td>329 ± 101</td>
<td>p&lt; 0.05</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.8 ± 1.6</td>
<td>11 ± 2.5</td>
<td>p&lt; 0.05</td>
</tr>
<tr>
<td>Serum Ferritin (ng/ml)</td>
<td>192 ± 32</td>
<td>368 ± 67</td>
<td>p&lt; 0.05</td>
</tr>
<tr>
<td>Serum Total Cholesterol (mg/dl)</td>
<td>232 ± 40</td>
<td>241 ± 36</td>
<td>p&gt; 0.05</td>
</tr>
<tr>
<td>Serum HDL Cholesterol (mg/dl)</td>
<td>44 ± 7</td>
<td>45 ± 9.3</td>
<td>p&gt; 0.05</td>
</tr>
<tr>
<td>Serum LDL Cholesterol (mg/dl)</td>
<td>145 ± 32</td>
<td>155 ± 28</td>
<td>p&gt; 0.05</td>
</tr>
<tr>
<td>Serum VLDL Cholesterol (mg/dl)</td>
<td>43 ± 17</td>
<td>41 ± 14</td>
<td>p&gt; 0.05</td>
</tr>
<tr>
<td>Serum Triglyceride (mg/dl)</td>
<td>124 ± 32</td>
<td>121 ± 35</td>
<td>p&gt; 0.05</td>
</tr>
</tbody>
</table>

This table shows that FBS, PP2BS, HbA1c and Ferritin are significantly high in patients of DM with CVD (Group III) than DM without CVD (Group II).

![Graph:1 Correlation of HbA1c & Ferritin in all study groups (n=150)](image-url)

r = 0.42
(moderate correlation)
p < 0.05
Graph: 2 Correlation of FBS & Ferritin in all study groups (n=150)

Graph: 3 Correlation of LDL & Ferritin in all study groups (n=150)

These graphs show that ferritin has good correlation with FBS and moderate correlation with HbA1c and LDL.

4. Discussion

Serum ferritin, a reflector of body iron stores was increased in diabetic patients compared to controls and this association was statistically significant. Subclinical hemochromatosis may contribute significantly for development of type 2 diabetes. Iron deposition occurs in various tissues and organs. In pancreas it may cause damage to β cell and decreased insulin secretion and in liver it may cause insulin resistance. In this study the significantly high (p<0.05) mean ferritin level in case group indicates etiological role of ferritin in development of diabetes mellitus and its cardiovascular complications.

Sumesh Raj et al. found that serum ferritin was significantly higher in the cases (p<0.01) when compared to controls which correlates with the present study (p<0.05) and found positive correlation between serum ferritin and FBS, HbA1c.

5. Conclusion

This study shows that there is significant increase in serum ferritin in diabetes mellitus compared to control group and hyper ferritinemia may be one of the causes for decreased insulin production and development of insulin resistance in diabetes mellitus. Serum ferritin also show moderate correlation with the lipid profile parameters which indicates dyslipidemia is present which is commonly associated with atherogenesis and can lead to coronary heart disease and its related morbidity and mortality. Serum Ferritin can be considered as routine diabetic biomarker and measures should be taken to decrease iron load in diabetic patients to improve glycaemic control and to prevent development of CVD because increased iron storage causes organ damage.

References

4. Ferritin ELISA (Solid phase direct sandwich ELISA method) kit inserts Mfg: DIA. Metra S.R.L.