Study of serum ferritin levels as an inflammatory marker and its relationship with Hba1c in type 2 diabetes mellitus

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Abstract  
Type 2 diabetes mellitus is the leading metabolic disorder globally as well as in India, affecting more than 135 million people all over the world.¹ Studies have shown a strong association between elevated serum levels of ferritin and type 2 DM.² Serum ferritin could be an independent determinant of poor metabolic control in the diabetic patient.³ Serum ferritin as an inflammatory marker in type 2 diabetes mellitus is an underutilized but can be a reliable tool to evaluate the metabolic disorder.⁴ We assessed 180 subjects (120 cases and 60 controls) in the current study. The case group was divided in to 2 groups based on the HbA1c levels as Group B: HbA1C < 6g/dl (60 cases) and Group C: HbA1C > 6g/dl (60 cases). The work embodied in the study includes subjects diagnosed of type 2 diabetes mellitus above 40 years of age, attending diabetic OPD in ESIC PGIMS R, of both gender. Group A (control) includes healthy adults above 30 years of age both the sexes. Serum levels Fasting sugar and Ferritin were estimated along with Glycated hemoglobin levels. Mean serum ferritin levels in Group A, Group B and Group C were 112.08 ± 90.1ng/dl, 334.4 ± 39.1ng/mL and 368.9 ± 46.7 ng/l respectively. Serum ferritin levels in Group B and C were significantly higher than Group A (p <0.001). The study concludes that inflammatory biomarker - ferritin is strongly and independently associated with cardiovascular complications in diabetes.

Keywords: Type 2 diabetes, Serum ferritin, Glycated hemoglobin, Inflammatory marker.

Introduction  
Type 2 diabetes mellitus is the leading metabolic disorder globally as well as in India affecting more than 135 million people all over the world.¹ Studies have shown a strong association between elevated serum levels of ferritin and type 2 DM. Serum ferritin could be an independent determinant of poor metabolic control in the diabetic patient.² There is enough evidence that shows Increased load of body iron stores causes oxidative stress which further leads to damage of beta cells of pancreas resulting in insulin deficiency.³

Frequent blood donation lead to decrease iron stores, which in turn reduces postprandial hyperinsulinemia and improves insulin sensitivity.⁴ Serum ferritin as an inflammatory marker in type 2 diabetes mellitus is an underutilized but can be a reliable tool to evaluate the metabolic disorder.⁴ There is a gap in information available regarding the poor control of blood glucose levels in diabetics with increased iron stores. Studies pertaining to this in Indian population are very minimal and finding out such correlation can be of high significance with the background of increased prevalence of anemia in the population.⁴

This study aims at estimating the levels of serum ferritin in patients of diabetes in order to establish its significance in the management and to prevent further complications.

Materials and Methods  
From the patients who attended the OPD with known diabetes in ESIC MS PGIMS R, Bangaluru, a total number of 180 subjects were included. This includes 60 controls Group A and 120 diabetic patients who were divided into 2 sub-groups - Group B: HbA1C < 6 mg/dl and Group C: HbA1C > 6mg/dl. Cases of type 2 diabetes of both gender in the age group >40 years attending diabetic OPD in ESIC PGIMS R, Rajajinagar, Bangalore, were included in the study. Patients with anaemia, thalassemia, Hemochromatosis, patients on drugs affecting serum ferritin levels, drug induced diabetes, pancreatic diseases (chronic pancreatitis), cystic fibrosis, endocrinopathies like cushing syndrome, thyrotoxicosis, acromegaly, gestational diabetes, patients with any other chronic infective & inflammatory conditions that may affect serum ferritin levels, were excluded from the study. The control group A includes healthy adult subjects in the age group > 30 years of both the sexes. A volume of 5ml venous blood sample was obtained after 12 hours overnight fasting and processed for the estimation of fasting blood glucose estimation, serum ferritin levels and HbA1C levels.

Serum concentration of glucose was estimated by using analytical kits from Erba Diagnostics Mannheim GmbH in semi-autoanaylzer (CHEM-5 Plus V2, Erba Mannheim). Serum concentrations of ferritin, insulin were estimated by Chemiluminescence immunoassay (CLIA) kits from Acculite Monobind in Lumax CLIA strip reader. Glycated hemoglobin was estimated by Nephelometry kits from Agappe in MISPA-i card reader.
Study of serum ferritin levels as an inflammatory marker

Prithvi Shankar et al.

Statistical Analysis
R software has been used for the statistical analysis. The correlations between HbA1c and serum ferritin levels have represented using “Scatter Plots” and the corresponding correlation coefficients (r) have been found out.

Results

Graph 1: Age distribution

![Age Distribution Graph]

P < 0.0908

Graph 2: Gender distribution

![Gender Distribution Table]

Graph 3: Fasting blood sugar levels (mg/dl)

![FBS Levels Graph]

FBS levels are positively correlated with HbA1c levels and statistically significant (P< 0.001)
Table 1: HbA1C Levels

<table>
<thead>
<tr>
<th>HbA1C Levels</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± S.D</td>
<td>5.01 ± 1.13</td>
<td>5.82 ± 0.16</td>
<td>8.59 ± 1.83</td>
</tr>
</tbody>
</table>

P < 0.0001

Graph 4: Distribution of serum ferritin levels in Group A, B & C

Table 2: Correlation of serum ferritin levels in Group A, B & C

<table>
<thead>
<tr>
<th>S. Ferritin (ng/dl)</th>
<th>Group A (n %)</th>
<th>Group B (n%)</th>
<th>Group C (n%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-100</td>
<td>40 (66)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>101-200</td>
<td>13 (23)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>201-300</td>
<td>2 (3)</td>
<td>44 (73)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>301-400</td>
<td>5 (8)</td>
<td>12 (20)</td>
<td>39 (65)</td>
</tr>
<tr>
<td>&gt;400</td>
<td>0</td>
<td>4 (7)</td>
<td>16 (27)</td>
</tr>
<tr>
<td>Mean ± S.D</td>
<td>112.08 ± 90.1</td>
<td>334.4 ± 39.1</td>
<td>368.9 ± 46.7</td>
</tr>
<tr>
<td>r value</td>
<td>0.48</td>
<td>0.361</td>
<td>0.55</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Graph 5: Scatter diagram - Correlation of HbA1c with serum ferritin levels in Group A, Group B and Group C

The serum ferritin levels are positively correlated with HbA1c levels and statistically significant.
Discussion

Type 2 diabetes mellitus is one of the largest metabolic disorders. Systemic inflammation is an 
predisposing factor for type 2 DM and atherosclerosis. Ferritin has been known as an index for body iron stores 
and also as an inflammatory marker.\(^2\)

In the present study, in Group B & C had 50 females 
and 70 males in the diabetic group and in Group A, 37 
were males and 23 were females.

We studied Glycated hemoglobin levels and serum 
ferritin in known type 2 diabetes subjects and healthy 
adults as controls.

In this study, 55% fell in the age group 41 to 50 
years mean age being 42.5 years in the group A. Whereas 
51.6% of subjects in the type 2 diabetic group were in 
the age group of 41-50 years with mean of 42.9 years age 
in diabetics with HbA1C <6mg/dl and 44.6 years in 
diabetics with HbA1C >6mg/dl.

In Group A, FBS levels were in the range of 87.74 
± 9.3 mg/dl. The mean ± SD of fasting serum glucose in 
Group B and Group C were 140.7 ± 17.3 mg/dl and 
167.85 ± 26.27 mg/dl, respectively. The mean value of 
fasting serum glucose was higher in Group B compared 
to Group C. The increase is found to be statistically 
highly significant (p <0.001) and is in accordance with 
previous studies.\(^5\)\(^7\)

Marginal elevation of glucagon, increased synthesis 
and decreased utilization of glucose induces increased 
blood glucose levels in type 2 diabetes.\(^8\) This leads to 
decreased utilization of glucose by the muscles and 
adipocytes and increased glucose synthesis by the liver 
and leading to hyperglycemia.

The mean ± SDs of HbA1c in controls was 5.01 ± 
1.13mg/dl & type 2 diabetes were in the range of 5.82 ± 
0.16 & 8.59 ± 1.83mg/dl in Group B & C respectively. 
The mean value of HbA1c was higher in type 2 diabetic 
subjects as compared to controls. The increase was 
statistically highly significant (p <0.001). This is in 
accordance with previous studies.\(^9\)\(^-\)\(^13\) It was also 
observed that HbA1c level positively correlated with 
fasting serum glucose. This is in accordance with 
Meshram A et al.,\(^14\) Shetty J K et al\(^9\) & Sultan S et al.\(^15\)

We also found statistically significant positive 
correlation existed between HbA1c and ferritin levels. 
This is in lieu with current consideration of serum ferritin 
levels as the best index of metabolic control for diabetic 
patients in clinical setting.\(^16\) It is also a predisposing 
factor in the risk of development of micro and 
macrovascular complications of type 2 DM.\(^17\)\(^18\)

The most important factor governing the quantity 
of glycated hemoglobin formed is the prevailing plasma 
glucose concentration. As the plasma glucose 
concentration is increased in diabetic subjects, glycated 
hemoglobin also increased in diabetic subjects.

Glycated hemoglobin levels probably reflect the 
degree of glycemic control of the individual better than 
measuring fasting and post-prandial blood glucose 
levels. This is because glycated hemoglobin does not 
depend on variables such as patient co-operation, time of 
the day, stress, exercise, food intake or renal threshold. 
This makes attractive screening test in population 
studies.\(^19\)

It represents the mean daily blood sugar 
concentration and degree of carbohydrate imbalance, 
better than fasting blood glucose concentrations or 
glucose tolerance test results. Hence it may provide a 
better index of control of diabetic patient without 
resorting to a glucose loading procedure.\(^20\)

The mean ± SDs of ferritin in controls was 112.08 ± 
90.1ng/dl and type 2 diabetic subjects were in the range 
of 334.4 ± 39.1ng/mL in diabetics with HbA1C < 6mg/dl 
and 368.9 ± 46.7 ng/ml in diabetics with HbA1C >6mg/dl respectively. The mean value of ferritin in type 
2 diabetic subjects was higher when compared to 
controls. Serum ferritin positively correlates with HbA1c 
in group B & C with r values of 0.36 and 0.55 for Group 
B and Group C respectively. The increase was found to 
be statistically highly significant (p <0.001). This is in 
accordance with Sumeet Smotra et al.\(^4\)

The mean value of ferritin in type 2 diabetic subjects 
was higher when compared to controls. The increase 
was found to be statistically highly significant (p <0.001). 
This is in accordance with the previous studies.\(^1\)\(^,\)\(^2\)\(^1\)\(^2\)

Excess iron deposition in the liver may cause IR by 
interfering with the ability of insulin to suppress hepatic 
glucose production. Iron is autoxidized to form highly 
reactive, lipid soluble iron-oxygen complexes. These 
free radicals are powerful pro-oxidants which can 
change membrane properties and result in tissue damage. 
In addition iron accumulation in hepatocytes may 
interfere with insulin extracting capacity of the liver, & 
affect insulin synthesis and secretion in pancreas. Iron 
excess probably contributes initially to IR and 
subsequently to decreased insulin secretion\(^21\)

According to our results together with previous 
other studies findings, we suggest that the quantitative 
determination of serum ferritin help in predicting type 2 
diabetes mellitus associated cardiovascular 
complications. Poorly controlled patients of DM have 
hyper ferritinaemia which co-relates with diabetic 
retinopathy, diabetic nephropathy and vascular 
dysfunction.

Glycated hemoglobin provides a retrospective index 
of glucose control over a time in diabetic subjects. 
Measurement of glycated hemoglobin serves as a simple 
and rapid procedure to assess glycemic control. It serves 
both as a screening test for control of diabetes and as an 
indicator of efficacy of treatment. Thus the study 
concluded that inflammatory biomarker - ferritin is 
strongly and independently associated with 
cardiopulmonary complications in diabetes. In addition 
regular exercises and effective administration of anti-
inflammatory agents may offer protection against type 2 
diabetes mellitus associated complications.
References