ESTIMATION OF SERUM FERRITIN LEVELS IN TYPE 2 DIABETIC PATIENTS AND ITS RELATION WITH HbA1C LEVEL.
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Article Info: Received 03 July 2019; Accepted 04 August. 2019
DOI: https://doi.org/10.32553/ijmbs.v3i8.456
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Conflict of interest: No conflict of interest.

Abstract
Background: Serum ferritin is known as an index for body iron stores also as an inflammatory marker and it is influenced by several disease. We were looking for a correlation between HbA1c and S. Ferritin in type 2 DM.
Methodology: The present study a total of 150 participants were enrolled of which 100 were confirmed cases of Type 2 Diabetes Mellitus and rest 50 age and sex matched healthy subjects constituted the control group. All were screened for HbA1c, Fasting blood sugar, Post prandial blood sugar and S.Ferritin.
Results: A highly significant variation and positive correlation was observed with respect to S.Ferritin and HbA1c levels. Mean S.Ferritin was high in the subgroup with poor glycemic control.
Conclusion: The fasting, post prandial sugar levels, HbA1c and S.Ferritin were significantly higher in the diabetic subjects. This study shows a positive correlation between HbA1c and S. Ferritin levels. So we can conclude that in diabetic patients S. Ferritin may serve as an independent marker of poor glycemic and metabolic control.
Keywords: Serum ferritin, Type 2 Diabetes Mellitus, HbA1c.

1. INTRODUCTION
Diabetes mellitus (DM) is one of the most prevalent endocrine disorders in the world (1). It is one of the most challenging health problems in today’s scenario (2). It comprises of a group of metabolic disorders sharing common phenotype of hyperglycemia (3). It belongs to a complex, chronic illness requiring continuous medical care and multifactorial risk reduction strategies beyond glycemic control.
According to American diabetes association 2011 hemoglobin A₁c (HbA₁c) which was primarily used as a test of glycemic control has now been added as a diagnostic test thus increasing its role than earlier. Glycated hemoglobin is produced by a ketoamine reaction between glucose and the N-terminal valine of both β-chains of the hemoglobin molecule. The major form of glycated hemoglobin is HbA₁c (4,5).
According to the American Diabetes Association (ADA) guidelines, the level of HbA₁c should be kept below 7% in all the diabetics (6). The level more than 7% indicate an increased chance of progression to the diabetic complications, mainly the micro vascular complications.
Serum ferritin is known as an index for body iron stores and also as an inflammatory marker. It is a multi-subunit containing protein, molecular weight of 450kD with the capacity to sequester up to 4500 atoms of iron in a ferrihydrite mineral core. It contains the enzyme ferroxidase that oxidizes ferrous iron atoms to ferric form (7). It serves to pack and isolate iron atoms thus preventing any toxic cellular damage by reactive oxygen species. It is commonly used test to evaluate iron homeostasis within the body (8).
Based on the observation that in patients with hereditary hemochromatosis, (which is characterized by extremely high levels of circulating ferritin) have high risk of complication by diabetes (9), several clinical studies have investigated the correlation of increased serum ferritin levels with an increased risk of future type 2 diabetes.
S.Ferritin levels may predict new cases of type 2 diabetes (10). Chronic, systemic subclinical inflammation has also been identified as a risk factor.
for insulin resistance, metabolic syndrome, and type 2 DM (11). The process of inflammation leads to hepatic synthesis of various acute phase proteins such as S.Ferritin which is supposed to play a role in insulin resistance as well as atherosclerosis. Increased incidence of type-2 diabetes mellitus (type 2 DM) has been seen to be related with high levels of serum ferritin. Increased S.Ferritin corresponding to body iron overload, is associated with insulin resistance measured in terms of elevated blood glucose and insulin levels. Long term micro vascular and macro vascular complications of diabetes may be due to raised S.Ferritin (12,13). The probable role of ferritin as an iron overload marker in pancreatic damage or peripheral insulin resistance results in hyper glycemia is not clear (14). There are no much studies to show the best cut-off value for serum ferritin in type 2 DM.

2. MATERIAL AND METHOD

The study was conducted in Department of General Medicine association with Department of Biochemistry in Mahatma Gandhi Medical College & Hospital, Sitapura, Jaipur. In the present study 100 cases were selected who met the criteria for recruitment and 50 control subjects were selected on random basis.

A study protocol was designed before undertaking this study, which was approved by the Institutional Ethics Committee vide letter No. MGMCH/IEC/JPR/2016/309 dated 22/06/2016 and informed consent was taken before enrolling the patients for the study.

Inclusion criteria

- Diagnosed cases of type 2 diabetes mellitus on treatment.
- Age between 40 to 60 years, either gender.
- Patients who are willing to participate and sign consent document.
- Patients willing to comply with the protocol requirements

Exclusion criteria

- Overt thyroid dysfunction
- Patients with type 1 diabetes mellitus
- Patients above 65 yrs age
- Chronic kidney disease
- On corticosteroid therapy
- Patients with acute or chronic liver disease, malignant process or inflammatory disease.
- Pregnant and lactating females
- Patients received recent iron therapy

Each enrolled patient was subjected to the detailed medical history, general physical examination and blood investigations including Fasting and PP blood glucose, HbA1c and S.Ferritin. An informed consent was taken before the collection of the sample from cases and controls. The control subjects had the same exclusion criteria as the cases and were not on any drug regimens which could influence the study.

3. RESULTS

Table 1: Mean FBS, PPBS, HbA1C, FERRITN (ng/dl) of subjects in Control and Diabetic Group

<table>
<thead>
<tr>
<th>S. NO.</th>
<th>PARAMETERS</th>
<th>CONTROL (50)</th>
<th>DM (100)</th>
<th>t-VALUE</th>
<th>P- VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>FBS (mg/dl)</td>
<td>92.3±14.50</td>
<td>136.68±54.00</td>
<td>-5.697</td>
<td>0.000</td>
</tr>
<tr>
<td>2.</td>
<td>PPBS (mg/dl)</td>
<td>113.0±10.07</td>
<td>214.5±73.43</td>
<td>-9.709</td>
<td>0.000</td>
</tr>
<tr>
<td>3.</td>
<td>HbA1c (%)</td>
<td>5.37±0.24</td>
<td>8.70±2.88</td>
<td>8.148</td>
<td>0.000</td>
</tr>
<tr>
<td>4.</td>
<td>S.FERRITN (ng/dl)</td>
<td>118.25±90.08</td>
<td>276.75±269.10</td>
<td>-4.047</td>
<td>0.000</td>
</tr>
</tbody>
</table>

The results obtained were presented as mean±SD and subjected to statistical analysis. All variable were compared among the diabetic and control group by applying student’s ‘t’ test. The fasting and post prandial sugar levels were significantly higher in the diabetic subjects. Mean HbA1c in the diabetic group was 8.70±2.88% as compared to 5.37±0.24% for the control group. The mean S. Ferritin level in the diabetic group was 276.75 ng/dl, which was more than twice the mean ferritin level of the normal control group.

Table 2: Mean distribution of FERRITN (ng/dl) according to HbA1c Levels

<table>
<thead>
<tr>
<th>GROUP</th>
<th>NO. OF CASES (N)</th>
<th>FERRITIN (ng/dl)</th>
<th>F-VALUE</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c ≤ 6</td>
<td>13</td>
<td>86.31±38.41</td>
<td>22.35</td>
<td>0.000</td>
</tr>
<tr>
<td>HbA1c (6.0-8.0)</td>
<td>41</td>
<td>156.28±137.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c &gt; 8.0</td>
<td>46</td>
<td>437.95±302.91</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The diabetic patients (n=100) were therefore divided into 3 subgroups based on HbA1c levels.

The variables were compared in the 3 groups by applying one way ANOVA test. A highly significant variation and positive correlation was observed among the 3 subgroups with respect to S.Ferritin levels. Mean S.Ferritin was as high as 437.95±302.91ng/dl in the subgroup with poor glycemic control (P=0.000). In the subgroup with HbA1c ≤ 6.0; the mean ferritin was 86.31±38.41ng/dl. The range of S.Ferritin in the 3 subgroups was

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>Ferritin Level (ng/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 6%</td>
<td>29.5 -150.0</td>
</tr>
<tr>
<td>6-8%</td>
<td>47.4 – 881.0</td>
</tr>
<tr>
<td>≥ 8.0</td>
<td>138.0 – 1000.0</td>
</tr>
</tbody>
</table>

4. DISCUSSION

DM is one of the most concern seeking health problems both in developing and developed countries. Type 2 DM has a multifactorial etiopathogenesis. The disease gains more attention due to the various complications associated with long standing DM. Besides duration, the average blood glucose levels also influence the prevalence of diabetes associated complications. Among various markers, HbA1c is most accurate marker of glycemic control nowadays.

Ferritin has gained recognition not only as an index of iron stores but also as a marker of inflammation (15). The present study was planned to assess the relation of S. Ferritin with glycemic index in type 2DM.

In 1999 a survey by Ford and his colleagues in United States on 9486 diabetic subjects show raised levels of S.Ferritin in diabetic subjects(16). According to studies by Kim et al., 2000 S.Ferritin may also be an independent marker of poor metabolic control in diabetic patients(15). Studies by F-Sharifi and Sh. Sazandeh, 2004 shows that S.Ferritin is higher in diabetics than in controls but its level has no correlation with blood sugar or HbA1c in diabetic patients.

Arul Senghor et al., 2012 showed that serum ferritin in diabetic patients is significantly higher and correlates with increased duration of diabetes. Similar Study by Raj S et al., 2013 showed that Serum ferritin, a reflector of body iron stores was markedly high in diabetic patients compared to controls and this significantly increased with increasing duration of diabetes(17). Also According to studies by Pramiladevi et al., 2013 serum ferritin was increased in diabetic patients as compared to controls(12).

The role of ferritin as an iron overload marker in pancreatic damage or peripheral insulin resistance resulting in hyper glycemia is not clear (14). The probable mechanism of elevated ferritin levels in diabetes is the oxidative stress caused by extracellular hyperglycemia which targets the pancreatic beta cells. Besides oxidative stress, transferrin undergoes glycation which decreases its ability to bind ferrous ion. This increased pool of free iron is diverted towards synthesis of ferritin (18). Besides comparing S.Ferritin in diabetic individuals and normal healthy subjects, the present study was planned to explore the relationship of S. Ferritin levels in diabetics with the glycemic index or precisely HbA1c levels.

In patients with type 2 diabetes mellitus, Eschwege E. et al., 1982 suggest to a positive correlation between increased serum ferritin and poor glycemic control, reflected by higher HbA1c. Cantur KZ et al., 2003 studies confirmed that poorly controlled diabetic patients had hyperferritinemia(19,20). In large population group Wrede CE et al., 2006 reported a significant correlation between S.Ferritin and the presence of insulin resistance criteria(21). Sumeet Smotra., R P Kudyar., 2008, found a positive correlation between increased S.Ferritin and poor glycemic control reflected by higher HbA1c. A positive and significant association between increased basal S.Ferritin levels and incident type 2 diabetes was observed by Chang Hee Jung et al., 2013. According to D Kundu et al., 2012 among the cases with poor glycemic control (>8% HbA1c), serum iron and serum ferritin levels were higher. Also Serum ferritin level is elevated in type 2 diabetes. In the present study S.Ferritin level is found to be higher in the newly diagnosed cases and low in patients suffering from long time diabetes.

Fernandez R et al., 2002 studied the impact of S.Ferritin reduction by bloodletting on insulin sensitivity and HbA1c levels in diabetic patients(22). In this study the positive effect of ferritin reduction on blood glucose control was used for confirmation of the probable role of ferritin in pathogenesis of diabetes. But bloodletting may affect total hemoglobin level and HbA1c as well, so using HbA1c as a marker of blood glucose control may not be appropriate.

Type 2 DM is recognized as a metabolic syndrome because it affects the various metabolic activities of the body. The treatment and management of diabetics focus is mainly on screening of the patient
with respect to development of diabetes associated complications. The usual screening of diabetics includes investigations like HbA1c, microalbuminuria and ACR. Screening for S.Ferritin has so far not been included in the diagnostic or follow up screening profile of diabetics. Thorough research on larger cohorts and Meta analysis with multicenter patients is therefore recommended to establish the importance of S.Ferritin estimation in type 2 diabetes patients. S.Ferritin should therefore be included in screening of diabetic patients. Moreover, its importance as diagnostic marker in patients with glucose intolerance should be further explored.

5. CONCLUSIONS

The present study was conducted at Mahatma Gandhi Medical College and Hospital jaipur to find a link between serum ferritin and DM and HbA1c, and to study the correlation between HbA1c and ferritin in type 2 diabetes mellitus (DM) patients. On comparing the variable between diabetic and control groups, the fasting and post prandial sugar levels and HbA1c levels were significantly higher in the diabetic subjects. The mean S.Ferritin level in diabetic group was 276.75ng/dl which was more than twice the mean ferritin level of the normal control group.

On the basis of HbA1c levels diabetic patients (n=100) were divided into 3 subgroups as HbA1c ≤6%, HbA1c 6-8% and HbA1c > 8%. Mean Ferritin of subjects in subgroup with poor glycemic control was as high as 437.95±302.91 ng/dl compare to subjects in the subgroup with HbA1c ≤ 6.0 mean ferritin was 86.31±38.41.

The study exhibited a positive correlation between S.Ferritin and HbA1c levels. It was observed that a poor glycemic control was favourable for elevation of S.Ferritin levels. This suggests that S.Ferritin may serve as an independent marker of poor glycemic and metabolic control in diabetic patients. So far, S.Ferritin has not gained recognition as a diagnostic tool in screening of diabetic patients. The present study recommends inclusion of S.Ferritin estimation in the screening of type 2DM patients as well as patients with impaired glucose tolerance.

References


