Assessment of Iron Status and Lipid Profile in Type 2 Diabetes Mellitus Patients with Non-Alcoholic Fatty Liver Disease

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ABSTRACT

Introduction: Non-alcoholic fatty liver disease (NAFLD) represents the hepatic manifestation of the metabolic syndrome which is characterized by obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia, with insulin resistance as a common feature. Lipid peroxidation and iron induced oxidative stress may play a role in NAFLD progression.

Aim and Objectives: 1. To assess the iron status in type 2 DM patients with NAFLD and compare it with T2DM patients without NAFLD. 2. To correlate the serum iron levels with lipid profile and markers of liver injury in T2DM patients with NAFLD.

Materials and Methods: 80 T2DM patients were screened for fatty liver by ultrasonography. Patients without fatty liver were considered as group I and with fatty liver as group II. Serum iron, TIBC, transferrin saturation, fasting blood glucose, AST, ALT, and lipid profile were analysed. Appropriate statistical analysis was done.

Results: Out of 80 Type 2 diabetic patients, 38 (48%) patients had fatty liver. NAFLD patients had significantly (p< 0.05) increased serum iron, triglyceride, total cholesterol, LDL-C, AST and ALT with decreased HDL-C when compared to group I. Fasting blood glucose and TIBC were not significantly different between the groups. Iron had a significant positive correlation with total cholesterol, triglycerides, LDL-C, AST and ALT.

Conclusion: A significantly altered iron status was observed in patients with NAFLD and iron levels were directly associated with the dyslipidemia and the liver enzymes.

Key words: Serum Iron, NAFLD, Lipid profile, Type 2 Diabetes mellitus.

INTRODUCTION:

Non-alcoholic fatty liver disease is a common condition characterized by excess of fat in liver which ranges from simple steatosis to steatohepatitis, cirrhosis and hepatocellular carcinoma (HCC) in the absence of excessive alcohol intake. The worldwide epidemic of obesity has led to a disturbing rise in the incidence of non-alcoholic fatty liver disease and its complications. Non-alcoholic steatohepatitis (NASH), the aggressive form of the disease, can lead to cirrhosis and liver failure. In India, the prevalence of NAFLD varies from 10% to 30% in the general population and increased in pre-diabetics and diabetics ranging 33-55%.

NASH can have a progressive course, the exact mechanism of this progression is not known. A “2-hit” hypothesis proposes a possible explanation for
the progression of NASH. In the first “hit” in NAFLD, is fat accumulation in the liver which typically occurs in the presence of insulin resistance. The increased hepatocyte fat impedes the mitochondrial function, resulting in lipid peroxidation. Moreover, the fatty acid-derived free radicals trigger cytokine production which then augments oxidative stress. In the second “hit”, lipid peroxides adversely affect adiponectin production and increase the levels of tumor necrosis factor. Thus, excessive fat accumulation and oxidative stress triggers liver cell necrosis and activation of hepatic stellate cells and consequently leading to fibrosis and ultimately to the development of cirrhosis. One of the potential cofactors suspected to enhance this oxidative stress is excessive hepatic iron accumulation. Iron may also contribute to liver injury in NAFLD by generating endoplasmic reticulum stress. In a mouse model of dietary iron overload and NAFLD, iron induced an unfolded protein response and endoplasmic reticulum stress. Noaki et al from Japan by using immunohistochemical staining of liver biopsy, concluded that iron overload may play an important role in the pathogenesis of NASH by generating oxidative DNA damage and iron reduction therapy may reduce hepatocellular carcinoma incidence in patients with NASH.

Based on this background, the present study was aimed to assess the iron status in type 2 DM patients with NAFLD and to correlate the serum iron levels with lipid profile and markers of liver injury in type 2 DM patients with NAFLD.

MATERIALS AND METHODS:

A cross-sectional study was conducted on 80 type 2 DM patients attending the Diabetic Out Patient Department of a tertiary care centre. Patients with history of jaundice / drug induced hepatitis, patients receiving hepatotoxic drugs, or iron supplementation, patients with alcohol consumption were excluded from the study. Institutional Ethical Committee (IEC) clearance was obtained. Written informed consent was obtained from all the patients after explaining the nature of the study. The fasting and post prandial venous blood samples were collected and serum was separated. The samples were analysed for fasting blood glucose (FBG) and post prandial blood glucose (PPBG), total cholesterol, triglycerides, HDL, serum iron, total iron binding capacity (TIBC), Aspartate transaminase (AST) and Alanine transaminase(ALT). All the biochemical measurements were done by using the auto analyzer (Roche® - Cobas® S) by standard methods. LDL-C was calculated using the Friedewald's formula. Transferrin saturation was calculated using formula TS = (Serum Iron / Total Iron Binding Capacity) x 100%. Enzyme activities were measured by kinetic methods based upon the recommendations of IFCC. All the type 2 diabetes patients were screened for fatty liver by ultrasonogram. Patients who had fatty liver by imaging were categorised as group II and patients without NAFLD as group I.

Statistical analysis:

All the statistical work was performed by the SPSS software. The results are presented as mean ± standard deviation. The frequency of NAFLD is shown as percentages. To estimate the differences between patients with and without NAFLD, the student's t-test was applied. Pearson's correlation analysis was used for analysing the association between iron and other parameters. A p-value of less than 0.05 was taken as significant.

RESULTS AND OBSERVATION:

Table 1 shows the grading of fatty liver using ultrasonography. Table 2 shows the comparison of
biochemical data between patients with and without NAFLD. T2DM patients with fatty liver had significantly increased PPBG, total cholesterol, triglycerides, LDL-C, serum iron, transferrin saturation, AST and ALT with significantly decreased HDL-C levels than the group 1. Fasting blood glucose and TIBC did not significantly vary between group I and group II.

Table 3 shows the correlation of serum iron with other biochemical parameters. Statistically significant positive correlation was observed between serum iron with total cholesterol, triglycerides, LDL-C, and AST. A negative correlation was observed for serum iron with HDL-C but it was not statistically significant. ALT showed a positive correlation which was not statistically significant.

Table-1: Ultrasonography Grading of Fatty liver

<table>
<thead>
<tr>
<th>Grading</th>
<th>No of cases (n=38)</th>
<th>Hepatomegaly (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>22</td>
<td>14</td>
</tr>
<tr>
<td>Moderate</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Severe</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>26 (68%)</td>
</tr>
</tbody>
</table>

Table-2: Comparison of biochemical data between group I and group II.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I Mean ± SD</th>
<th>Group II Mean ± SD</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG (mg/dl)</td>
<td>141±33</td>
<td>152.0±44.63</td>
<td>0.16</td>
</tr>
<tr>
<td>PPBG (mg/dl)</td>
<td>245.4±45.94</td>
<td>274.9±53.19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>210.7±37.42</td>
<td>273.4±44.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>144.6±26.02</td>
<td>269.8±54.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>48.2±9.41</td>
<td>40.7±9.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>126.8±37.27</td>
<td>190±42.46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum iron (µmol/l)</td>
<td>16.3±2.88</td>
<td>19.9±2.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIBC</td>
<td>67.3±8.2</td>
<td>64.3±9.2</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>23.1±5.1</td>
<td>26.8±4.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>19.6±8.65</td>
<td>34.8±17.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>23.78±12</td>
<td>38.13±21.85</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

DISCUSSION:

The current epidemics of obesity and diabetes among adults and children residing in both developed and developing countries had shown increased prevalence of NAFLD over time. The prevalence of NAFLD in type 2 diabetes mellitus patients was 48% in the present study population which is similar to a study done in India by Gupta et al.\(^\text{10}\) with 49% and in a study conducted in New Delhi by Agarwal et al.\(^\text{11}\) with 57.2%. Another study by Ijaz-ul-Haque et al.\(^\text{12}\) from Pakistan had also reported the frequency of NAFLD as 51% in type 2 diabetes mellitus. Leite et al.\(^\text{13}\) found a 78% NASH prevalence at the histological examination in nearly 100 patients with T2DM and ultrasonography evidence of NAFLD. Hepatomegaly is a common finding among NAFLD which occurs in 75% of cases\(^\text{14}\) whereas hepatomegaly was found in 68% of NAFLD patients in our study.

Hypertriglyceridemia have been strongly correlated with liver fat accumulation\(^\text{15}\). Clark et al.\(^\text{15}\) had reported that hypertriglyceridemia occurs in 20% to 80% of NAFLD patients\(^\text{16}\). In the present study, a significantly higher triglyceride, total cholesterol and LDL-C levels with lower HDL-C was observed in T2DM patients with NAFLD than without NAFLD. These results are consistent with the studies by Somalwar AM et al.\(^\text{15}\) and Ashwani Guleria et al.\(^\text{17}\) as they had reported that patients with NAFLD had significantly higher levels of serum
were observed in NAFLD patients when compared to type 2 diabetes patients without fatty liver. In a prospective cohort study done by Mattias et al, NAFLD patients with elevated liver enzymes are associated with a clinically significant risk of developing end stage liver disease. Various studies had reported raised enzyme levels ALT, AST and GGT were hardly more than twice the normal and this level of difference was of no use for practical diagnostic purposes; however their levels are known to fluctuate. Significant positive correlation of ALT and AST with serum iron was observed in our study population. Tiikkainen et al had reported that there was a correlation of ALT activity even within normal range with increasing hepatic fatty infiltration.

CONCLUSION:

The present study has demonstrated that type 2 diabetes patients with NAFLD had increased serum iron with pronounced dyslipidemia. Role of serum iron in the causation of fatty liver has been established by its direct association with the lipid profile and markers of liver injury. Limitations:

The smaller sample size limits our study and further studies with larger population should confirm the role of iron in T2DM patients NAFLD.

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