Association of serum uric acid level in Non Alcoholic Fatty Liver Disease.

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Abstract:
ABSTRACT Background Non-alcoholic fatty liver disease (NAFLD) is a cause of fatty liver, occurring when fat is deposited (steatosis) in the liver not due to excessive alcohol intake. NAFLD is considered a hepatic manifestation of the metabolic syndrome. Worldwide prevalence of non-alcoholic fatty liver disease is 38 percent. Serum uric acid level has been suggested to be associated with factors that contribute to insulin resistance and metabolic syndrome.
Aim The aim of this study is to investigate the association of serum uric acid level and body mass index (BMI) with non-alcoholic fatty liver disease.
Methods This observational study was conducted in subjects who attended the master health check up clinic of PSG hospitals. 50 subjects with NAFLD and 50 non fatty liver subjects were included in the study. NAFLD was diagnosed based on the abdominal ultrasonographic finding. Serum uric acid level and body mass index (BMI) was also measured. Uric acid quartiles were categorized into four groups and the number of subjects who came under each group was noted.

Results The BMI was compared between cases and controls. The mean Body Mass Index (kgm) for cases was 27.01 with SD 3.53 and for controls was 23.91 with SD 3.11. Elevated BMI is associated with increased incidence of NAFLD with a significant p value of less than 0.05. The mean uric acid concentration (mgdl) for cases is 5.73 with SD 1.57 and for controls is 4.69 with SD 0.91. Increased serum uric acid concentration is associated with increased incidence of NAFLD with a significant p value of less than 0.05.

Conclusion This study showed elevated BMI is associated with increased incidence of NAFLD. Serum uric acid levels are significantly associated with NAFLD and high uric acid levels showed high incidence of NAFLD compared to low serum uric acid level.

Keyword :NAFLD, uric acid, body mass index
Introduction:
Uric acid is the major end product of purine metabolism and is formed from xanthine by the action of xanthine oxidoreductase. Serum uric acid level is maintained by the balance between uric acid production and excretion. Non alcoholic fatty liver disease is defined as a diffuse accumulation of fat in the liver, after excluding alcohol intake and other causes of liver disease. NAFLD has clinical importance because of its increasing prevalence and its potential to become advanced cirrhosis and hepatic failure. Identifying risk factors is essential for prevention of NAFLD. The exact risk factors for NAFLD have not been fully clarified. Recent studies showed that NAFLD is closely associated with obesity, hypertension, dyslipidemia, and glucose intolerance, a cluster of disorders now recognized as metabolic syndrome. For this reason NAFLD has been considered as the hepatic manifestation of metabolic syndrome.

In previous studies, an association between serum uric levels and metabolic syndrome has been reported. The association between serum uric acid and chronic liver disease has also been reported in United States, which leads us to speculate that there might be a relationship between uric acid concentrations and NAFLD among the indians. The aim of this study is to evaluate the serum uric acid levels with NAFLD in comparison to normal BMI and elevated BMI. The serum uric acid level may act as a useful clinical predictor for assessing the risk of NAFLD.

Materials and Methods:
This study was conducted after getting clearance from Ethics committee. Written informed consent was also obtained from subjects before participation in the study.

Study Design and Subjects:
This observational study was conducted in subjects undergoing Master Health Checkup in PSG Hospitals. Totally 50 subjects (cases) of both sex in the age group of 31-60 with NAFLD were included in this study. We also included 50 normal subjects with non fatty liver (controls) of both sex in the same age group.

Inclusion Criteria:
NAFLD subjects
Both male and female
Age group 31 – 60 years

Exclusion Criteria:
Smoking
Alcohol consumption
Diabetes mellitus
Hypertension
Past history of liver disease such as hepatitis
Hepatotoxic drugs

Baseline Examinations:
The subjects were instructed to fast for at least 12 hours prior to examination, refrain from exercise during the day before examination. Baseline examinations included a medical history and health habit inventory taken by investigator, anthropometric measurements, hepatic ultrasonic examination result and serum uric acid result.

Standing height and body weight were measured without shoes. Body Mass Index (BMI, kg/m²), used as an index of body fat, is calculated as weight in kilograms divided by height in meter square. BMI in the range of < 18.5 kg/ m² is considered as underweight, 18.5 to 24.9 kg/ m² is considered as normal, > 25 to 30 kg/ m² is considered as overweight, > 30 kg/ m² is considered as obese.
Baseline ultrasound abdomen examination was carried out by trained radiologist. Hepatic steatosis was diagnosed by characteristic echo patterns, such as evidence of diffuse hyperechogenicity of the liver and poor visualization of intra-hepatic structures. Hyperuricemia is defined as serum uric acid level 7 mg/dl in men and 6.0 mg/dl in women.

To explore the association between serum uric acid level and NAFLD, subjects were divided according to their serum uric acid levels. Serum uric acid quartiles were defined < 5.0, 5.1 - 6.0, 6.1 - 7.0, > 7 mg/dl for men and < 4.0, 4.1 - 5.0, 5.1 - 6.0, > 6.0 mg/dl for women.

**Results:**

The mean Body Mass Index (kg/m²) for group I (NAFLD) is 27.01±3.53 and for group II (No Fatty Liver) is 23.91±3.11. The mean Uric acid concentration (mg/dl) for group I is 5.730±1.571 and for group II is 4.696±0.914.

Table 1 shows the comparison of BMI between group 1 and group II with a highly statistical significance of p < 0.05. BMI is an independent factor, if it is increased the chance of developing NAFLD is also associatively increased.

**Table 1:**
Association of Body mass index (BMI) in NAFLD (Group 1) and in Non fatty liver (Group II)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I (N=50)</th>
<th>Group II (N=50)</th>
<th>Chi square value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &gt; 25</td>
<td>31</td>
<td>17</td>
<td>7.853</td>
<td>&lt; 0.05*</td>
</tr>
<tr>
<td>BMI &lt; 25</td>
<td>19</td>
<td>33</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant.

Table 2 shows the comparison of serum uric acid level between group I and group II which is higher in group I with a p value of < 0.05 which is also statistically significant than group II. This proves higher the uric acid level the greater the chances of developing NAFLD.

**Table 2:**
Association of serum uric acid in NAFLD (Group 1) and in Non fatty liver (Group II)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I (N=50)</th>
<th>Group II (N=50)</th>
<th>Chi square value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypouricemia</td>
<td>26</td>
<td>12</td>
<td>7.173</td>
<td>&lt; 0.05*</td>
</tr>
<tr>
<td>Normal uric acid</td>
<td>24</td>
<td>38</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant.

As already mentioned about uric acid quartiles for better association, only 15% of group I subjects come under 1st quartile as compared to 66% in group II which indicates the low uric acid level in the control group (group II) which is depicted in fig 1. 52% of group I subjects come under 3rd quartile as compared to 11% in group II which is shown in fig 2. This shows, higher the uric acid levels higher the chances of developing NAFLD. The percentage of subjects in 4th quartile for group I and group II were 16% and 5% respectively. There was not much difference in percentage (17% & 18% respectively) of subjects in 2nd quartile in both groups.
Figure 1 Percentage of subjects in 1st quartile (Low) of serum uric acid level in group 1 and group II

Figure 2 Percentage of subjects in 3rd quartile (High) of serum uric acid level in group 1 and group II

Discussion:
NAFLD is now recognized worldwide as an important cause of chronic liver disease. We observed independent association between serum uric acid concentrations and the presence of NAFLD. Our results are in agreement with previous studies. Serum uric acid was independently associated with biopsy-proven hepatic steatosis in a study of 1915 Chinese patients aged 12-80 years with chronic hepatitis B infection. Li et al. also reported similar results in a study of 8925 apparently healthy Chinese.

Same mechanism could explain the significant relationship between serum uric acid and NAFLD, current understanding of the progression of NAFLD involves the “2-hit hypothesis”. The “first hit” is excessive fat accumulation in hepatocytes, which is closely linked to insulin resistance. Numerous studies have introduced significant association between serum uric acid concentration and the metabolic syndrome and its components, where insulin resistance is the primary problem. The significant association between serum uric acid and NAFLD suggest that insulin resistance is a possible mechanism linking serum uric acid with NAFLD.

The “second hit” is the process from oxidative stress to hepatocyte injury, inflammation and fibrosis. Excessive free fatty acids in hepatocytes of patients with NAFLD generate an excess of reactive oxygen species (ROS) leading to lipid peroxidation of hepatocytes, cytokine production and hepatic inflammation.

An experimental study has shown that serum uric acid stimulates the synthesis of macrophage chemo-attractant protein, interleukin-1, interleukin-6 and tumor necrosis factor (TNF-) all of which are pro-inflammatory molecules and stimulate production of CRP in the liver. So major factors connecting increased serum uric acid concentration with NAFLD may be due to oxidative stress and chronic low grade inflammation.

In this study we included BMI to show the strong association between BMI and NAFLD because BMI has already been shown to be associated with NAFLD in previous studies.

Conclusion:
This study clearly demonstrates that serum uric acid is a significant factor associated with the development of NAFLD. It is necessary to analyze serum uric acid when a person is incidentally diagnosed to have NAFLD because recent studies in the past has proved hypouricemic therapy clinically lowers serum uric acid levels, which significantly ameliorated hepatic steatosis. Liver biopsy is gold standard for diagnosis of fatty liver but because of its invasiveness we followed ultrasonography which is non-invasive, safe, widely available and sensitive method for detecting hepatic steatosis.

References:


