Abstract

Objective: The objective of this study is to evaluate the correlation of radiologically diagnosed non-alcoholic fatty liver disease (NAFLD) with serum uric acid (SUA) levels.

Methods: It is a case control study conducted in private sector tertiary care hospital. A total of 200 subjects were involved in this study after calculation of sample size. The study participants were recruited from the medicine ward while the healthy controls were taken from the general population. Non probability consecutive sampling technique was employed. Inclusion criteria was patients who were diagnosed with fatty liver through abdominal ultrasonography. Exclusion criteria was patients suffering from any other chronic illness that can lead to an echogenic liver on ultrasound (viral hepatitis and diabetes) and history of alcohol consumption. Ethical approval for the study was taken from IRB. Data were entered and analysed using IBM SPSS version 23.0. Mean with standard deviation for age, BMI, SBP, DBP and SUA were reported between two study groups.

Results: Highly significant results were observed between two groups; diseased and controls. Mean uric acid levels were found to be significantly higher in NAFLD (non-alcoholic fatty liver disease) cases as compared to controls, with serum uric acid showing an affirmative and positive linear relationship with fatty liver. An increase in BMI and systolic and diastolic blood pressures was also seen in NAFLD group as compared to controls which indicates that BMI is a comorbid for cardiac complications among the NAFLD patients.

Conclusions: The study determined that uric acid levels elevate with progression of non-alcoholic fatty liver disease. This finding brings a new insight of uric acid in clinical practice. Increase in serum uric acid levels might serve as a trigger for physician to screen for NAFLD. An increase in BMI and systolic and diastolic blood pressure in NAFLD patients indicates underlying causes leading to cardiovascular complications in these patients.

Keywords: Non-alcoholic fatty liver disease, uric acid, body mass index.

Introduction

With an increase in metabolic syndrome and obesity, NAFLD has become one of the most com-
monly occurring chronic liver disorders across the world\(^1\). NAFLD is characterized by excessive deposition of triglycerides in the liver cells which may range from simple steatotic changes to non-alcoholic steatohepatitis (NASH), fibrosis, and eventually lead to liver cirrhosis which may progress to hepatocellular carcinoma (HCC)\(^2\). NAFLD is among the most prevalent hepatic diseases in the Western countries. About 20%-30% of the population is affected by it. NAFLD is among the most prevalent problems of the Asia-Pacific region and its prevalence is expected to increase in future because of the rapidly changing lifestyles and dietary habits\(^1,3\).
NAFLD is a complication of metabolic syndrome (MetS) involving the liver. Uric acid is formed as the final metabolic end product of purine metabolism and is a strong predictor of metabolic syndrome. Disorders of purine metabolism cause hyperuricemia, which has a close association with NAFLD. NAFLD is prevalent among the general population ranging from 20%-30% and up to 75%-100% in individuals suffering from obesity. As the dietary patterns and lifestyle are changing, increase in the incidence of NAFLD has emerged as a serious community health concern. Increased serum uric acid (SUA) levels and increased triglycerides have independently been known to be associated with fatty liver. Identification and early detection of risk factors leading to the development of NAFLD is vital for its prevention. The pathogenesis of NAFLD involves a series of physiologic and biochemical events. These events include various hereditary and environmental factors and factors related to metabolism and stress-related factors. Excessive intake of foods rich in purine, endogenously produced purine and purine metabolic end products lead to the production of uric acid. All cells of the body need a well-balanced number of purines for growth, reproduction and existence. Uric acid which is final metabolic end product of purine metabolism is excreted via the kidneys and the rest enters into the intestinal tract via the bile duct and is decomposed by intestinal bacteria. When the amount of uric acid production exceeds the amount of its excretion, the level of uric acid in the body is elevated. Studies have found that consuming energy rich foods with high purine content can result in metabolic syndrome and fatty liver disease because they also increase triglyceride production. Moreover, in individuals having metabolic abnormalities increased synthesis of triglycerides also leads to increased SUA production. In addition to this inflammatory mediator such as tissue necrosis factor, which induces apoptosis and oxidative stress, have been proposed to be important factors that lead to damage to the hepatocellular architecture and function. The association between uric acid and NAFLD has been demonstrated by many clinical and epidemiological studies. It has been seen that increased serum uric acid levels often coexist with insulin resistance, coronary artery disease, visceral obesity and low high-density lipoprotein levels. Inflammation and oxidative stress are hypothesized to be the important link in this relationship. Accumulating evidence has shown that the SUA level is an independent predictor of increased prevalence of NAFLD. As discussed in earlier studies, while staying in the almost normal range not only frank hyperuricemia but also SUA levels showed a positive correlation with metabolic syndrome.

The correlation between serum uric acid and NAFLD is demonstrated by the '2-hit' theory. Deposition of fat inside hepatocytes is the first damage, due to which the hepatocytes become more susceptible to get damaged by other stressful triggering factors, which include inflammation, insulin resistance and obesity. Among these factors, insulin resistance has a major role in promoting lipolysis of the adipocytes hence increasing the influx of free fatty acids in the liver. Thus, resistance to insulin causes hyperinsulinemia, increasing the production of uric acid and decreasing its renal clearance. Obesity, a public health problem worldwide leads to hyperuricemia and metabolic syndrome. A negative correlation is seen between insulin resistance and reduced renal clearance of uric acid, which is itself associated with increased levels of serum uric acid.

Early identification of individuals who are at risk for developing fatty liver disease is essential for early diagnosis and prevention especially through lifestyle modifications. For the prevention and diagnosis of NAFLD researches on the relationship between SUA and NAFLD are important.

The aim of this study was to identify relationship between uric acid levels and NAFLD (Non-alcoholic fatty liver disease). The detection of this association is important because NAFLD can lead to many metabolic abnormalities. This study will help in prompt detection and treatment of NAFLD.
Subjects and Methods

A case control study was conducted in Sharif Medical city hospital, which is a private sector tertiary care hospital located in Lahore, Pakistan from January 2018 to November 2018.

Sample size was calculated using open epi website calculator. A sample size of 200 subjects was calculated which were further subdivided into 2 groups. GROUP A: 100 healthy controls with no history of alcohol intake or any chronic illness. GROUP B: 100 subjects who were diagnosed as having fatty liver disease on ultrasound but with no history of alcohol intake.

Inclusion criteria included patients of age group 18 to 60 years, both male and female, group B comprised all subjects who had been diagnosed with fatty liver disease on ultrasound. Exclusion criteria excluded all patients having history of alcohol intake, history of drug abuse and history of hepatitis A,B or C. Non probability consecutive sampling technique was utilized for selection of participants. Biochemistry lab investigations were measured in both groups. Hypertensive cut-off was taken for systolic BP 140 mmHg and diastolic BP at 90 mmHg. Ethical permission for the present study was taken from ethical review board. Data which was obtained during the study was kept confidential.

Blood samples were taken from subjects after informed consent. Serum uric acid was analysed using The Uric Acid Assay Kit Catalog Number STA-375 using a sensitive quantitative fluorometric assay for measuring uric acid concentrations.

Body mass index was calculated by the following formula;

$$\text{Body mass index (BMI)} = \frac{\text{Weight in kilograms}}{(\text{height in meter})^2}$$

Ultrasonography of the liver has a sensitivity of 82 to 89 percent and a specificity of 93 percent for identifying fatty liver infiltrate. On Ultrasound, fatty liver is identified as a bright liver having more echogenicity than that of the right kidney. The grading system of steatosis is from mild, moderate and severe steatosis.

Mild steatosis: Increased echogenicity of liver, normally seen diaphragm and intra hepatic vessels.

Moderate steatosis: Moderately increased echogenicity, mildly obscured visualization of diaphragm and intra hepatic vessels.

Severe steatosis: Significantly increased echogenicity, obscured penetration, poor or non-visualization of diaphragm and intrahepatic vessels.

Data was entered and analysed using IBM SPSS version 23.0. Mean with standard deviation for age, BMI, SBP, DBP and SUA were reported between two study groups. Independent sample t-test was used to compare these mean levels among cases and controls. Pearson Correlation was done to find the any relationship of NAFLD with SUA. p-values <0.05 were considered as significant. Pie chart and scatter diagram also given for graphical presentation of data.

Results

In the present study there were two hundred samples equally distributed into two study groups cases and controls. The proportion of females in control group (A) was 62% and among diseased group (B) it was 41%. NAFLD was classified as mild, moderate or severe depending upon the echogenicity seen on ultrasound. Figure 1 shows the percentage of gradings of NAFLD in group B, 18% was mild, 41% were moderate and 41% were severe grade of NAFLD. In Figure: 2 Scatter plot was used to show correlation between NAFLD and SUA levels. A positive correlation was seen between SUA and NAFLD using Pearson's correlation considered significant using Independent sample t-test Mild NAFLD in 18%, Moderate NAFLD in 41% and severe NAFLD in 41%.
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>GROUP(A)</th>
<th>GROUP(B)</th>
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<tbody>
<tr>
<td></td>
<td>(n=100)</td>
<td>(n=100)</td>
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<tr>
<td>Age (years)</td>
<td>Mean 41.9</td>
<td>Mean 46.6</td>
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<td></td>
<td>SD 5.4</td>
<td>SD 5.8</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>Mean 25.1</td>
<td>Mean 32.1</td>
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<tr>
<td></td>
<td>SD 1.4</td>
<td>SD 5.3</td>
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<tr>
<td>SBP (mmHg)</td>
<td>Mean 117.6</td>
<td>Mean 153.5*</td>
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<tr>
<td></td>
<td>SD 9.0</td>
<td>SD 8.4</td>
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<tr>
<td>DBP (mmHg)</td>
<td>Mean 76.4</td>
<td>Mean 96.3*</td>
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<td></td>
<td>SD 8.0</td>
<td>SD 7.6</td>
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<tr>
<td>Serum uric acid (µmol/L)</td>
<td>Mean 236.6</td>
<td>Mean 355.7*</td>
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<td></td>
<td>SD 39.0</td>
<td>SD 40.2</td>
</tr>
</tbody>
</table>

*p<0.05 was

Discussion

Recent evidence suggests that NAFLD should be considered a risk factor for cardiovascular disease (CVD). NAFLD is a strong clinical signal for insulin resistance and metabolic syndrome (MetS). Fatty liver is considered a confirmative risk factor for diabetes mellitus type 2. Our study showed that increase in SUA level in cases of NAFLD as compared to normal controls. This study shows the correlation between elevated SUA levels and NAFLD that has been conducted in Pakistan. The correlation among SUA and NAFLD was significant and was not dependent upon anthropometric variables like gender, age and all other clinical variables. These associations provide a strong basis for correlation between SUA and NAFLD. Hence serum uric acid can be used as an independent marker and a diagnostic tool for the assessment of fatty liver disease. This association between SUA and development of NAFLD give an indication that increased SUA levels may have a role in the progression of NAFLD. Two underlying causes can explain the mechanism by which high SUA levels leads to the development of NAFLD. One is that uric acid is an oxidant and in metabolic syndrome it potentiates oxidative stress. The second cause is that the production of uric acid by the enzyme xanthine oxidoreductase leads to the formation of reactive oxygen species which cause further oxidative damage leading to damage to healthy cells. Hence increase in serum uric acid levels lead to oxidative stress induced complications to the liver cells and hence is an important causative factor and marker of NAFLD. Studies conducted previously also give results similar to our results. Some studies proved that serum uric acid level is an unconventional marker and risk factor for detection of NAFLD in individuals who are at a risk of developing the disease and presented it as an important measure in the diagnosis of NAFLD. In clinical practice detection of fatty liver is usually an incidental finding while performing ultrasound abdomen for some other cause, as serum uric acid is significantly correlated with fatty liver disease, all individuals presenting with fatty liver on ultrasound must be...
tested for serum uric acid levels and all individuals presenting to physicians with elevated serum uric acid levels must be tested radiologically for presence of fatty liver disease. Further research should be conducted in finding out the effects of treatment on lowering serum uric acid levels on fatty liver disease progression. This association is also important in detecting hyperuricemia in patients who have been diagnosed with NAFLD on ultrasonography. In our study systolic and diastolic blood pressures were also establish to be significantly greater in NAFLD group as compared to controls, this shows the association of fatty liver disease with cardiovascular complications. Increased triglycerides and LDL-C in these patients also contribute to these cardiovascular complications. This may occur due to excessive deposition of fat in vessels and heart. Further the oxidative role of uric acid may contribute to enhanced lipid peroxidation leading to development of atherosclerosis. An increase in BMI was also seen in NAFLD group. It has been demonstrated a statistically significant, correlation between BMI and NAFLD in individuals who have no metabolic illness. NAFLD is associated with increased deposition of triglycerides in hepatocytes which is explained by this increase in BMI in these patients. Weight loss and exercise have been shown to reduce liver enzyme levels and steatosis in children and adults who are obese. Hence restricted diet and exercise are advised in NAFLD individuals. Bayard et al.,(2006) has shown in his study that treatment of insulin resistance has improved disease oriented outcomes in patients with non-alcoholic fatty liver disease. Medications for treating hyperlipidaemia also have improved biochemical and histologic findings in patients with non-alcoholic fatty liver disease.

This study has some limitations. We made the diagnosis of hepatic changes in NAFLD on the basis of ultrasonography, which is not a sensitive method for determining mild steatosis. However, it is a safe and reliable method for detecting hepatic steatosis in most of the epidemiological surveys for detection of NAFLD.

Conclusion

NAFLD is associated with an increase in serum uric acid levels and an increase in BMI as well as systolic and diastolic blood pressures. Serum uric acid shows a positive correlation with NAFLD severity and can be used as a predictor and marker in the screening and diagnosis of fatty liver disease.

Conflict of Interests

Authors have no conflict of interests and received no grant/funding from any organization.

References

9. Kumar A, Singh AK, Panda PK, Nischal N, Soneja M. Non-alcoholic fatty liver disease diagnosis,


