

Original Research Article

Correlation of Radiologically Diagnosed Non Alcoholic Fatty Liver with Serum Uric Acid Levels

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Abstract

This study was to assess the correlation of radiologically diagnosed non alcoholic fatty liver disease with serum uric acid levels. It was a case control study conducted in a private sector tertiary care hospital in 2018. 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. Cases included 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. Highly significant difference was observed in mean serum uric acid levels and BMI in cases as compared to controls, with serum uric acid showing a positive linear relationship with fatty liver. Serum uric acid levels elevate with the progression of non alcoholic fatty liver disease. This finding brings a new insight of uric acid in clinical practice. Increased in serum uric acid levels might serve as a trigger for physician to screen for NAFLD.

Keywords: Non alcoholic fatty liver, serum uric acid, BMI.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a pathological change in liver architecture, but without history of excessive alcohol intake (Alvarez-Lario and Macarron-Vicente, 2010). NAFLD can be considered as a hepatic presentation of metabolic syndrome (MetS). NAFLD includes many metabolic disturbances, such as hyperuricemia, insulin resistance, obesity, diabetes mellitus type 2, and hyperlipidemia, all of which are the features of metabolic syndrome. 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. Researchers have shown that increased serum uric acid levels can lead to NAFLD by promoting endoplasmic reticulum stress, oxidative stress and insulin resistance. However, the association

between NAFLD and hyperuricemia is still controversial (Browning et al., 2004). With the increasing trend of obesity and metabolic syndrome, NAFLD has become one of the most commonly occurring chronic liver disorders across the world. NAFLD is prevalent among the general population ranging from 20%-30% and up to 75%-100% in individuals suffering from obesity (Chang et al., 2016). As the dietary patterns and lifestyle are changing, increase in the incidence of NAFLD has emerged as a serious community health concern. 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) (Day and James, 1998).

Increased serum uric acid (SUA) levels and increased triglycerides have independently been known to be associated with fatty liver. 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 amount of purines for growth, reproduction and existence (Li et al., 2009). Uric acid 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 (Choi and Diehl, 2008; Cohen et al., 2011). 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 (Darmawan et al., 2017). Moreover in individuals having metabolic abnormalities increased synthesis of triglycerides also leads to increased SUA production (Jensen et al., 2018). In addition to this inflammatory mediators such as tissue necrosis factor α which induces apoptosis and oxidative stress, have been proposed to be important factors that lead to damage to the hepatocellular architecture and function (Kumar et al., 2017). 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 (Day and James, 1998). Accumulating evidence has shown that the SUA level is an independent predictor of increased prevalence of NAFLD (Browning et al., 2004).

The correlation between serum uric acid and NAFLD is demonstrated by the '2-hit' theory (Lee et al., 2019). Deposition of fat in the hepatocytes is the first "hit", which causes the hepatocytes to become more susceptible to more damage due to other stressful triggering factors, which include inflammation, insulin resistance and obesity. Among these factors, insulin resistance has a major role in promoting lipolysis of peripheral adipose tissue and increase in the influx of free fatty acids in the liver. Thus insulin resistance causes hyperinsulinemia, which increases the production of uric acid and decreases the renal clearance of uric acid (Lee et al., 2010; Lima et al., 2015). Obesity, a public health problem worldwide leads to hyperuricemia and metabolic syndrome (De Oliveira and Burini, 2012). 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 (Gaggini et al., 2013).

Early identification of individuals who are at risk for developing fatty liver disease is essential in for early diagnosis and prevention especially through life style

modifications. Therefore, the research on the relationship between SUA and NAFLD has important significance for the prevention and diagnosis of NAFLD.

METHODOLOGY

A case control study which was conducted in a private sector tertiary hospital located in Lahore, Pakistan during the year 2018.

Sample Size

Sample size was calculated using open epi website calculator using a reference study.

Reference Study

Yang C, Yang S, Feng C, Zhang C, Xu W, Zhang L, et al. (2018) Associations of hyperuricemia and obesity with remission of nonalcoholic fatty liver disease among Chinese men: A retrospective cohort study. *PLoS ONE* 13(2)

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 was subjects 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 was all subjects 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 cutoff was taken for systolic BP 140 mmHg and for diastolic BP at 90 mmHg (Chopra and Ram, 2019). Ethical permission for the present study was taken from ethical review board. Data which was obtained during the study was kept confidential.

Ultrasound

Ultrasonography of the liver has a sensitivity of 82 to 89 percent and a specificity of 93 percent for identifying fatty liver infiltrate (Bayard et al., 2006). On Ultrasound, fatty liver is identified as a bright liver having more

Table 1. Baseline Characteristics of Studied Samples

Characteristics	Controls (n=100)		Cases (n=100)		p-value
	Mean	SD	Mean	SD	
Age (years)	41.9	5.4	46.6	5.8	<0.01*
BMI (kg/m ²)	25.1	1.4	32.1	5.3	<0.01*
SBP (mmHg)	107.6	9.0	133.5	8.4	<0.01*
DBP (mmHg)	66.4	8.0	76.3	7.6	<0.01*
Fasting plasma glucose(mmol/L)	5.4	0.4	6.0	0.6	<0.01*
Triglycerides mmol/l(mmol/L)	1.2	0.1	3.1	0.5	<0.01*
Total cholesterol(mmol/L)	6.3	0.2	7.1	0.4	<0.01*
HDL(mmol/L)	1.3	0.2	0.9	0.2	<0.01*
LDL(mmol/L)	2.7	0.4	3.4	0.4	<0.01*
BUN(mmol/L)	5.2	0.7	6.1	0.4	<0.01*
serum uric acid (μmol/L)	236.6	39.0	355.7	40.2	<0.01*
AST(mmol/L)	19.2	5.5	34.4	4.4	<0.01*
ALT(mmol/L)	27.7	4.0	36.0	2.8	<0.01*

*p<0.05 was considered significant using Independent sample t-test

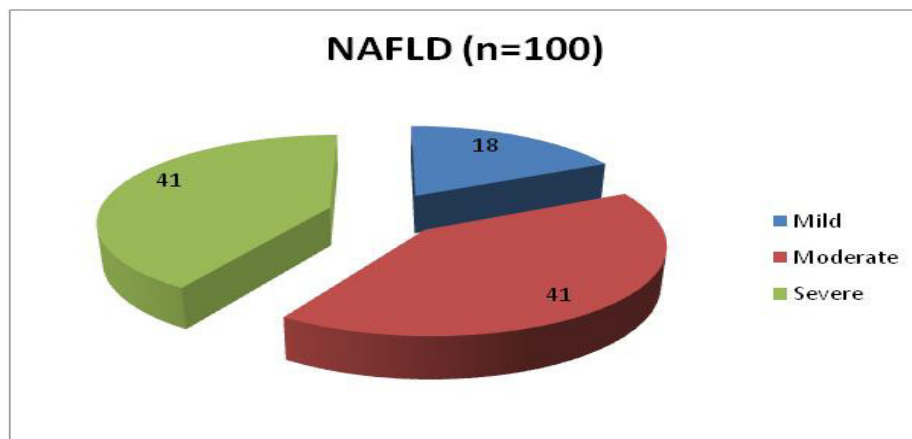


Figure 1. Pie Chart for NAFLD severity based on ultrasound in group B

echogenicity than that of the right kidney (Pratt and Kaplan, 2000). USG has specificity of 85-95% for fat detection, while sensitivity varies with amount of fat (55% for 10-20% fat and 80% for greater than thirty percent fat, giving overall sensitivity of 65%-95%). The grading system of steatosis is as follows:

Mild steatosis: Increased echogenicity of liver, normally seen diaphragm and intra hepatic vessels (Kumar et al., 2017).

Moderate steatosis: Moderately increased echogenicity, mildly obscured visualization of diaphragm and intra hepatic vessels (Kumar et al., 2017).

Severe steatosis: significantly increased echogenicity, obscured penetration, poor or non-visualization of diaphragm and intrahepatic vessels (Kumar et al., 2017).

Statistical Analysis

Data were stored and analyzed using IBM SPSS version

23.0. Mean with standard deviation for age, BMI, SBP, DBP and Lipid profiles 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 baseline characteristics and lipid profiles. P-values less than 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 was 62% and among cases it was 41%. Table 1 reports the mean and standard deviations of baseline characteristics and biochemical variables.

NAFLD was classified as mild, moderate or severe

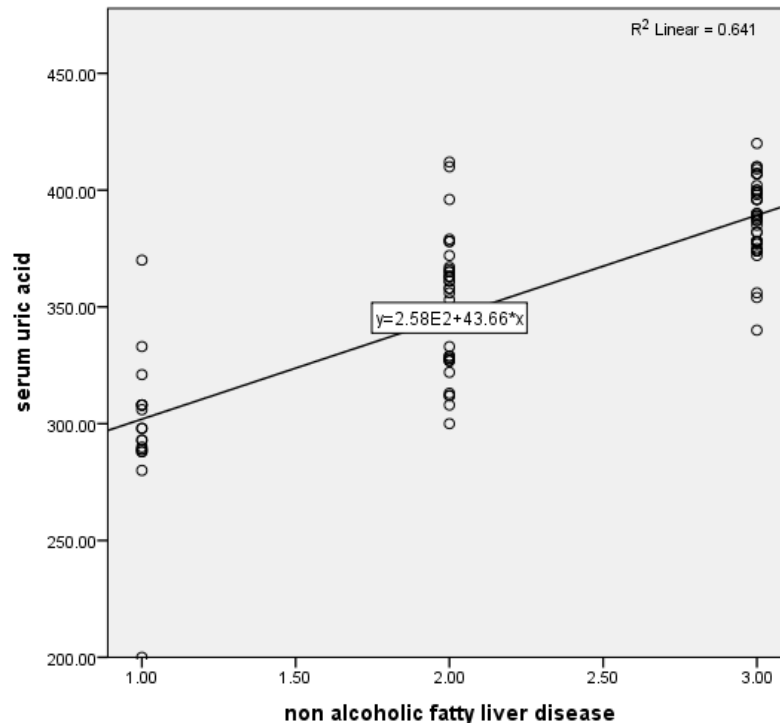


Figure 2. Scatter Plot: Correlation of SUA and NAFLD

depending upon the echogenicity seen on ultrasound (Pratt and Kaplan, 2000). Pie chart gives the percentage of NAFLD cases, 18% was mild, 41% were moderate and 41% were severe cases of NAFLD. Figure 1

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. Figure 2

DISCUSSION

Recent evidence suggests that NAFLD should be considered a cardiovascular risk factor. NAFLD is a strong clinical signal for insulin resistance and MetS, and is considered a confirmative risk factor for diabetes mellitus type 2 (Lee et al., 2019). Our study showed that increase in SUA level is correlated with NAFLD. To the best of our knowledge, this is the first study that shows the correlation between elevated SUA levels and NAFLD that has been conducted in Pakistan. The association between SUA and NAFLD was significant even in the normal range of SUA and was independent of baseline gender, age, metabolic syndrome, and all other clinical variables. These results provide novel evidences for a significant association between SUA and development of NAFLD. Studies conducted previously also give results similar to our results (Xu et al., 2010). 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 (Quiñones et al., 1995; Sonsuz et al., 2000). NAFLD is the most common cause of elevated liver enzymes. Serum ALT level is a part of the initial screening test for liver function testing. Its elevation demonstrates increased fat accumulation in the liver (Williams et al., 2011). The most common cause for unexplained and persistent elevation of ALT is NAFLD (Xie et al., 2013). An elevation of serum ALT levels (less than twice the normal value) is of great clinical significance in the diagnosis of NAFLD if other causative factors of elevated serum aminotransferase levels, have been ruled out (Yang et al., 2018). Our results also showed an elevation in serum AST levels in NAFLD patients. The results of our study are similar to Lee et al. (2019) who has shown an increase in serum aminotransferase levels in NAFLD patients. Serum triglycerides, serum LDL and total serum cholesterol were also found to be significantly higher in NAFLD group as compared to controls. On the other hand serum HDL was lower in the NAFLD group. Many studies have shown that NAFLD is associated with insulin resistance. Insulin resistance decreases the antilipolytic effects of insulin in the peripheral adipose tissues along with an increase in the levels of free fatty acids. The elevation of free fatty acids leads to mitochondrial and endoplasmic dysfunction leading to the development of lipotoxicity (Zhang et al., 2017). In addition to this, fat accumulation in vessels, heart and pancreas leads to complications in these viscera (Zhang et al., 2017). In our study systolic and diastolic blood pressures were also found to be

significantly higher in NAFLD group as compared to controls, this shows the association of fatty liver disease with cardiovascular complications due to excessive deposition of fat in vessels and heart. An increase in BMI was seen in NAFLD group. Chang et al. (2016) has demonstrated a statistically significant, correlation between BMI and NAFLD in individuals who have no metabolic illness. Weight loss and exercise have been shown to reduce liver enzyme levels and steatosis in children and adults who are obese (Bayard et al., 2006). Bayard et al. (2006) has shown in his study that treatment of insulin resistance has improved disease oriented outcomes in patients with nonalcoholic fatty liver disease. Medications for treating hyperlipidemia also have improved biochemical and histologic findings in patients with nonalcoholic fatty liver disease (Bayard et al., 2006).

CONCLUSION

NAFLD is associated with an increase in serum uric acid levels, elevation of serum aminotransferases, dyslipidemia 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 INTEREST

There is no conflict of interest between the authors.

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