

Original Research Article

A study of the association of serum uric acid levels with alanine aminotransferase and gamma-glutamyl transferase levels in non-alcoholic fatty liver disease patients diagnosed by imaging studies

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is a condition defined by excessive fat accumulation in the form of triglycerides (steatosis) in the liver. In recent years, an association between elevated serum uric acid concentrations and NAFLD has been reported. The aim of the study was to perform cross-sectional study to determine the association between serum uric acid levels and the levels of serum alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT), in NAFLD patients.

Methods: In this hospital-based cross-sectional study, 300 patients with diagnosed NAFLD were included during the one-year period from July 2015 to June 2016.

Results: Elevation of alanine aminotransferase levels was seen in a total of 93 cases (31%) and elevation of GGT levels in NAFLD patients was seen in 112 patients out of a total of 300 (37.33%). Hyperuricemia was observed in 99 cases out of a total of 300 cases of NAFLD (33%). A significant association was observed between the two parameters.

Conclusions: The prevalence rate of NAFLD was significantly higher in subjects with hyperuricemia than that in those without hyperuricemia (78.19% versus 40.83%) ($p < 0.001$), and the prevalence rate increased with progressively higher serum uric acid levels ($p < 0.001$). The relationship between rising uric acid levels with rising ALT and GGT levels in these patients was also found to be statistically significant.

Keywords: Cirrhosis, Hyperuricemia, Liver failure, Non-alcoholic fatty liver disease, Steatosis

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a condition defined by excessive fat accumulation in the form of triglycerides (steatosis) in the liver (>5% of hepatocytes histologically).¹ Sub-groups of NAFLD patients have liver cell injury and inflammation in addition to the accumulation of excessive fat (steatohepatitis). The latter condition, designated non-alcoholic steatohepatitis (NASH), is virtually indistinguishable histologically from alcoholic steatohepatitis (ASH) and is characterized by the presence of ballooning degeneration and lobular inflammation with or without peri-sinusoidal fibrosis in addition to steatosis.² While the simple steatosis seen in NAFLD does not correlate with increased short-term

morbidity or mortality, progression of this condition to that of NASH dramatically increases the risks of cirrhosis, liver failure and hepatocellular carcinoma (HCC); cirrhosis due to NASH being an increasingly frequent cause of liver transplantation. NASH is also widely considered to be the hepatic expression of the metabolic syndrome.¹ Risk factors for development of non-alcoholic steatohepatitis include obesity, especially central adiposity, glucose intolerance or type 2 diabetes mellitus (T2DM), hypertension and dyslipidemia.³

NAFLD is the cause of asymptomatic elevation of aminotransferases in 42-90% of cases once other causes of liver disease are excluded, characterized typically by a hepatocellular pattern of liver-related enzymes with mild

elevations (1-2 times the upper limit of normal) in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST).⁴ Despite having the disease, up to 50% of NAFLD patients can have normal ALT and AST levels.^{5,6}

Hyperuricemia has also been implicated in the development of hypertension, kidney disease, metabolic syndrome, and cardiovascular disease (reviewed by Feig et al and Edwards).⁷ Although hyperuricemia has traditionally been considered a result of these conditions or an epiphenomenon, mechanisms have been proposed by which hyperuricemia could actually cause them. Such mechanisms include the induction of endothelial dysfunction, insulin resistance, oxidative stress, and systemic inflammation, which are now known to be important risk factors for the development or progression of most liver diseases. For example, these conditions are considered central in the pathogenesis of NAFLD and NASH. Therefore, it is hypothesized that hyperuricemia, which strongly reflects and may even cause oxidative stress, insulin resistance, and systemic inflammation, is a risk factor for the development of cirrhosis or the presence of hepatic necroinflammation.⁷ In recent years, an association between elevated serum uric acid levels and ALT and GGT levels in NAFLD patients has been reported. However, no study from the North-Eastern part of the country has yet been done to determine this association. The aim of the study was to perform a cross-sectional study to determine the association if any, between increased serum uric acid levels and serum alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) levels in NAFLD patients in Assam Medical College and Hospital, Dibrugarh.

METHODS

The study was conducted in Assam Medical College and Hospital during a period of one year from July 2015 to June 2016. A total of 300 patients were taken up for the study (via systemic random sampling) from the inclusion criteria as mentioned below and data was collected using a pretested proforma meeting the objectives of the study. It was seen from previous admission registers of the medicine department that on an average of around 600 cases of NAFLD were admitted in one year for the past five years (2010-2014). Thus, the size of the sample in this study was taken to be 300 cases with every second case of NAFLD being taken up for the study to remove the selection bias.

Inclusion criteria

The study consisted of all patients >13 years of age diagnosed as NAFLD cases, who presented to the medicine outpatient and inpatient department, as well as the gynecology outpatient department. These included type 2 diabetics, overweight and obese individuals (BMI ≥ 25 kg/m²), and females with polycystic ovarian disease (PCOD).

Exclusion criteria

The study excluded patients with age <13 years, history of alcohol abuse, liver disorders (cirrhosis, Wilson's disease, hepatitis etc.), renal disorders, congestive cardiac failure, pregnant women, women on oral contraceptive pills, and patients with intake of hepato-toxic drugs. Also excluded patients with known history or diagnosed cases of gout or rheumatoid arthritis.

Ethical clearance was obtained from the Institutional Ethics Committee of Assam Medical College and Hospital before initiation of the study, and an informed consent was obtained from the participating subjects.

Serum uric acid estimation in biochemistry lab by enzyme uricase assay in accurex

For this study, the normal reference values for uric acid were taken as 3.4-7.2 mg/dl and 2.4-6.1 mg/dl for males and females respectively while for hyperuricemia, values for males and females were taken as >7.2 mg/dl and >6.1 mg/dl respectively as per the standardized reference values from the biochemistry laboratory in Assam Medical College and Hospital, Dibrugarh.⁸

Serum GGT estimation in biochemistry lab

Gamma-glutamyl transferase reagent is used to measure the transferase activity by an enzymatic rate method. The normal reference values as taken from Assam Medical College and Hospital Biochemistry Laboratory were 5-85 U/l.⁹

Serum ALT estimation in biochemistry lab

The kinetic method by TC matrix system automatically proportions the appropriate sample and reagent volumes into the cuvette. The system monitors the change in absorbance at 340 nm. This change in absorbance is directly proportional to the activity of alanine aminotransferase in the sample and is used by the TC matrix system to calculate and express alanine aminotransferase activity. The normal reference values from Assam Medical College and Hospital Biochemistry Laboratory were 12-78 U/l.⁹

Diagnosis of fatty liver by ultrasound abdomen

Ultrasonography of the abdomen was done using the MINDRAY Z6 ULTRASOUND machine, and the diagnosis of fatty liver by ultrasound was made on the basis of the increased echogenicity of the liver parenchyma. Ultrasound is a useful but imperfect tool in evaluating diffuse liver disease having sensitivity for detecting hepatic steatosis ranging from 60 to 94% and the specificity from 84 to 95%.¹⁰ The normal echogenicity of the liver is determined by comparing the liver echogenicity with that of the cortex of the kidney, and increased liver echogenicity can be taken as a reliable criterion for

diagnosing fatty liver.

Statistical methods

Student paired t-test (Two tail type 3) were used to compare the baseline patient characteristics and to find out the significance of the association between serum uric acid levels and ALT and GGT levels.

RESULTS

Table 1 shows that the study group comprised of 300 patients with a mean age of 47.31 ± 12.26 years. In the study group, majority of the patients (36.67%) were in the age group of 40-49 years (N=110). In our study group, 41.33% were males (N=124) and 58.67% were females (N=176). A female predominance was noted. Majority of the patients i.e.; 79% (N=237) were in the overweight category while 21% (N=63) of patients were found to be in the obese category I.

Table 1: Age, sex and BMI distribution in NAFLD patients.

Characteristics	N
Age (years)	
<20	1
20-29	18
30-39	60
40-49	110
50-59	59
60-69	33
>70	19
Gender	
Male	124
Female	176
BMI (kg/m²)	
<25	0
25-29.9	237
30-34.9	63
35-39.9	0
>40	0
Total	300

From Table 2 it was deduced that out of a total number of 124 male patients, 107 were found to be diabetic (86.29%), and out of total 176 female patients, 116 (65.91%) were found to be diabetic cases.

Elevation of alanine aminotransferase levels was seen in a total of 93 cases (31%) of NAFLD while elevation of GGT levels was seen in 112 out of a total of 300 patients (37.33%) as shown in Table 3.

From Table 4, hyperuricemia (elevation of uric acid levels) was seen in 38 out of 124 male patients of NAFLD (30.65%). Out of a total of 176 female NAFLD patients, hyperuricemia (elevation of uric acid levels) was observed

in 61 female patients (34.66%).

Table 2: Sex distribution in diabetics and non-diabetics.

Sex	Diabetics (N= 223)		Non-diabetics (N= 77)		Total (N)
	N	%	N	%	
Males	107	86.29	17	13.71	124
Females	116	65.91	60	34.09	176
Total	223	74.33	77	25.67	300

Table 3: Serum ALT and GGT levels in NAFLD patients.

Variables	ALT (U/l)		GGT(U/l)	
Range	12-78	>78	5-85	>85
Number (N)	207	93	188	112
Total	300		300	

Table 4: Serum uric acid levels in males and females.

Variables	Uric acid levels (mg/dl)			
Sex	Male		Female	
Range	3.4-7.2	>7.2	2.4-6.1	>6.1
Number (N)	86	38	115	61
Total	124		176	

Table 5 shows the association of hyperuricemia with various parameters in female and male NAFLD patients. Elevated uric acid levels were seen to be significantly associated with increasing age and BMI (p value<0.001 for both) as well as with type 2 diabetes (p value<0.001). There was also a statistically significant association seen between elevated uric acid levels and ALT and GGT levels (p value<0.05 for both); ALT levels were elevated in 21 out of 61 female patients (34.43%) with hyperuricemia with a mean value of 78.34 ± 31.34 U/l and a median value of 66 U/l and GGT levels elevated in 20 out of 61 female patients (32.79%) with hyperuricemia with a mean value of 100.28 ± 44.43 U/l and a median value of 80 U/l. In males, ALT levels were elevated in 17 out of 38 male patients (44.74%) with hyperuricemia with a mean value of 77.95 ± 24.62 U/l and a median value of 73.5 U/l and GGT levels elevated in 15 out of 38 male patients (39.47%) with hyperuricemia with a mean value of 97.95 ± 45.61 U/l and a median value of 81 U/l. No such significance was seen with AST levels (p value>0.05).

Table 6 shows the relationship between NAFLD and increased uric acid levels; hyperuricemia was observed in 99 out of a total of 300 cases of NAFLD (33%), with a statistically significant association between the two (p value<0.001).

Table 7 shows the relationship between serum uric acid levels and ALT and GGT levels; 38 NAFLD patients had elevation of ALT levels along with hyperuricemia with a mean ALT value of 110.53 ± 16.69 U/l as compared to a mean value of 94.33 ± 11.49 U/l in patients with normal

serum uric acid levels (N=55). Thus, a significant association between serum uric acid and ALT levels was observed (p value<0.001). 35 NAFLD patients had elevation of GGT levels along with hyperuricemia with a mean GGT value of 158.57±19.97 U/l as compared to a

mean value of 124.96±20.42 U/l in patients with normal serum uric acid levels (N=77). Thus, a significant association between serum uric acid and GGT levels was observed (p value<0.001).

Table 5: Association of various parameters in NAFLD patients with elevated uric acid levels in females and males.

Clinical characteristics	Hyperuricemia (females)		P value	Hyperuricemia (males)		P value
	Yes (N=61)	No (N=115)		Yes (N=38)	No (N=86)	
Age, mean±SD (years)	57.72±12.43	43.21±11.28	<0.001	51.18±9.95	43.70±9.25	0.00019
BMI, mean±SD (kg/m ²)	29.85±1.77	27.42±1.47	<0.001	30.03±1.41	27.79±1.67	<0.001
ALT, median (range) (U/l)	66 (36-143)	57 (32-127)	0.013	73.5 (42-121)	56 (34-116)	0.0011
AST, median (range) (U/l)	34 (15-173)	37 (15-101)	0.55741	33.5 (20-78)	37 (18-148)	0.21881
GGT, median (range) (U/l)	80 (45-202)	66 (15-178)	0.03285	81 (21-176)	67 (24-162)	0.01498
TLC, mean±SD (per cu mm)	7332.79±2183.10	6909.57±2384.56	0.23818	6055.26±2306.24	6846.51±2299.04	0.08222
Diabetes mellitus, N (%)	53 (86.89)	63 (54.78)	0.00019	37 (97.37)	70 (81.39)	0.01712

Table 6: The association between NAFLD and serum uric acid levels.

Variable	Total number of cases	Hyperuricemia		P value
		Present N (%)	Absent N (%)	
NAFLD	300	99 (33)	201 (67)	<0.001

Table 7: The association of serum uric acid levels with ALT and GGT levels.

Association parameter	Elevated ALT (U/l)		Elevated GGT (U/l)	
	With hyperuricemia (N=38)	Without hyperuricemia (N=55)	With hyperuricemia (N=35)	Without hyperuricemia (N=77)
Mean±SD	110.53±16.69	94.33±11.49	158.57±19.97	124.96±20.42
P value	<0.001		<0.001	

DISCUSSION

The present study was carried out in three hundred cases of NAFLD to study the association of hyperuricemia and increased alanine aminotransferase ALT and GGT levels in patients diagnosed as NAFLD by imaging studies. All the cases fulfilled the inclusion and exclusion criteria of the study as per the methodology.

The mean age of the patients in this study was 47.31±12.26 years. The mean age of male NAFLD patients was found to be 45.99±10.04 years while that of female NAFLD patients was 48.24±13.56 years. These statistics were in accordance with a cross-sectional and prospective study by Kojima et al in 2003, where it was found that NAFLD had maximum prevalence in the 4th and 5th decades of life while it declined in those in the 6th and 7th decades. Fan et al in 2005 found that the prevalence of fatty liver increased

with age in both sexes, peaking in women 60-69 years of age, and in men 40-49 years of age while Zelber et al in 2006 and Zhou et al in 2007 also found NAFLD prevalence to be maximum in the age group of 40-60 years.¹⁰⁻¹³

The prevalence of increased uric acid levels in the NAFLD population enrolled in our study was found to be 33% (99 patients out of a total of 300) which included 38 (12.66%) out of 124 male patients and 61(20.33%) out of 176 female patients. The association was observed to be statistically significant (p<0.001). This was in accordance with previous studies such as those done by Sertoglu et al in 2014 where the prevalence of hyperuricemia was found to be 33.4%.¹⁴ Petta et al observed that about 20% of the patients in his study group had hyperuricemia, that was independently associated with younger age and lobular inflammation.¹⁵

In our study we found a statistically significant association of serum uric acid levels and ALT and GGT levels in patients with NAFLD. The association between raised serum uric acid levels and ALT and GGT levels was previously shown in a prospective observational study done by Xu et al in 2010 where it was observed to be significant.¹⁶ In the study titled 'Profile of liver enzymes in non-alcoholic fatty liver disease in patients with impaired glucose tolerance and newly detected untreated type 2 diabetes' done by Sanyal et al in 2015, the elevation of serum ALT and GGT levels was shown to be significantly associated with NAFLD, but no such comparison between ALT, GGT and serum uric acid levels was shown.¹⁷

In the study done by Afzali et al in 2010, data was derived from the first National Health and Nutrition Examination Survey (NHANES I) and also from the NHANES II (1988-1994) study and NHANES III (1999- 2006) study to determine whether the serum UA level was associated with elevated serum ALT or GGT, two markers of hepatic necro-inflammation.¹⁸ The study showed that a higher serum uric acid level was associated with greater mean serum ALT and GGT levels and a greater probability of elevated serum ALT and GGT which led to the conclusion that the serum uric acid level is associated with the development of cirrhosis and the presence of elevated serum liver enzymes after adjustments for important causes and risk factors of chronic liver disease. An independent association between elevated uric acid levels and ALT levels was also shown in a study done by Lee et al in 2010 where the results were statistically significant.¹⁹ Also, a significant association between serum uric acid and liver enzymes was also shown by Shih Ming et al in a US based study in 2015.²⁰

Our study was in accordance with these studies as well as with the most recent study done by Chen et al, where a total of 7.4% participants had elevated ALT levels and the prevalence of hyperuricemia was 14.9% in males and 7.3% in females.²¹ There was a significantly positive association between SUA levels and the prevalence of elevated ALT levels.

However, this study was not without limitations. Firstly, liver biopsy is regarded as the gold standard for the diagnosis of NAFLD, our diagnosis was based on Ultrasonographic examination, which is not able to differentiate non-alcoholic steatohepatitis from fibrosis, and has an alleged sensitivity of 67-89% and specificity of 77-89%. Secondly, the amount of alcohol intake and exercise was measured by a questionnaire so that it is likely that this method introduced a measurement bias. Finally, we did not adjust for lifestyle or dietary factors, such as meat and fructose intake that may contribute to increased uric acid levels and NAFLD.

CONCLUSION

Our findings demonstrated a significant association

between serum uric acid levels, ALT and GGT levels in NAFLD patients in a small North-Eastern Indian population. These findings were consistent with the reported trends in other studies and were supported by some experimental evidence which shows that Intracellularly, uric acid may have a pro-inflammatory and pro-oxidant role. Although Hyperuricemia has previously been clearly associated with alcohol consumption, obesity, insulin resistance, systemic inflammation, and metabolic syndrome, the associations that our study has described with elevated liver enzymes (ALT and GGT) persisted after adjustments for these conditions.

Further studies are needed to investigate whether this association is causal and has any clinical utility in the prediction of the presence or incidence of NAFLD, as observational studies such as ours cannot definitively distinguish between these two possibilities. If this is confirmed, further consideration can be given to measures that reduce the serum uric acid levels as a means of preventing NAFLD in patients with elevated levels of uric acid and liver enzymes.

Hyperuricemia is seen to be significantly associated with NAFLD. Increased uric acid levels share a significant association with elevated levels of ALT and GGT in patients with NAFLD. Further consideration can be given to measures that reduce the serum uric acid levels as a means of preventing NAFLD in patients with elevated levels of uric acid and liver enzymes.

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