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STUDY OF ASSOCIATION BETWEEN SERUM URIC ACID LEVELS AND CHRONIC LIVER DISEASE

[1]Pradeep Kumar Gupta, [2]Himanshu Agarwal, [3]Saurabh Singhal, [4]Keerti Manocha

[1]Professor, Department of General Medicine, Subharti Medical College, Meerut, Uttar Pradesh, India
[2]Resident, Department of General Medicine, Subharti Medical College, Meerut, Uttar Pradesh, India
[3]Professor and HOD, Department of General Medicine, Subharti Medical College, Meerut, Uttar Pradesh, India
[4]Senior Resident, Department of General Medicine, Subharti Medical College, Meerut, Uttar Pradesh, India
Corresponding Author: Himanshu Agarwal (him199212@gmail.com)

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Abstract

Aim: *To find the level of uric acid in patients of chronic liver disease and its correlation, if any, with etiology and other parameters.*
Materials and Method: *This was a prospective study conducted on North Indian population admitted in Department of Medicine during the period of 2020 and 2021. A total number of 50 patients diagnosed with chronic liver disease were included in this study. A detailed history was elicited from the patients regarding their present complaints; associated symptoms; alcohol intake, smoking, previous history of hypertension, diabetes mellitus, arthritis, hypothyroidism, any cardiac illnesses and chronic drug intake. All patients underwent an ultrasonogram abdomen and estimation of serum uric acid levels. Waist circumference in males and females was measured. Glycemic and Body mass index were recorded. Serum uric acid level was sent for analysis on the day of admission and was followed up.*
Results: *Out of 50 subjects, 38 (76%) were males and 12 (24%) were females. Mean ± SD uric acid (mg/dl) among the study subjects was 6.69±2.92. Normal uric acid (3.1-5) was revealed among 24% of the subjects while higher uric acid/hyperuricemia was reported among 38 (76%) subjects. Mean uric acid was 4.03, 5.17 and 8.94 among the subjects having CTP class A, B and C respectively. Pearson correlation analysis revealed significant positive correlation between uric acid and total bilirubin, SGOT, SGPT and CTP Score.*
Conclusion: *Elevated serum uric acid level might be a risk factor for the incidence of chronic liver disease. Hyperuricemia may act as a surrogate marker for assessing the prognosis of CLD.*

Keyword: *Uric acid, CLD, CTP, SGOT, SGPT*

Introduction:

Liver is a complex organ with interdependent metabolic, excretory and defence function. The use of different screening tests improves the detection of hepatobiliary abnormalities and help differentiates the basis for clinically suspected disease and determine the severity of the liver disease [1, 2].
In humans and higher primates, uric acid (UA) is the final oxidation product of purine metabolism and is excreted in urine. Hyperuricemia has long been recognized as a cause of gouty arthritis and kidney stones. More recently, hyperuricemia has also been implicated in the development of hypertension, kidney disease, metabolic syndrome, and cardiovascular disease [3-5]. 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 by hyperuricemia of endothelial dysfunction, insulin resistance, oxidative stress and systemic inflammation [5].
Oxidative stress, insulin resistance and systemic inflammation are now known to be important risk factors for the development or progression of the most important liver diseases. For example, these conditions are considered central in the pathogenesis of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) [6]. In addition, they contribute to the progression of hepatitis C virus (HCV)-related and alcoholic liver diseases [7].
In chronic liver disease, there is progressive damage to liver parenchyma with subsequent loss of function. In chronic liver disease of different etiologies, uric acid levels are found to be high. In cases of non-alcoholic fatty liver disease (NAFLD), high uric acid levels are considered as independent etiological risk factors [8]. Also, a high uric acid level is known effect of alcohol metabolism and thus, hyperuricemia may be found in alcoholic liver disease [9, 10]. In different biological studies, UA levels have been found to correlate directly with the level of tissue damage [11]. Compared to the serum levels, the tissue levels of UA may be even better predictors of

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tissue injury. Thus, UA may be considered as a marker of tissue damage. We therefore undertook this study to find the level of uric acid in patients of chronic liver disease and its correlation, if any, with etiology and other parameters.

Materials and Methods

This was a prospective study conducted on North Indian population admitted in Department of Medicine during the period of 2020 and 2021. A total number of 50 patients diagnosed with chronic liver disease were included in his study. The subjects having age group of more than 18 years and suffering from chronic liver disease were included. Moribund patients, patients on allopurinol/febuxostat/thiazides/furosemide, patients on chemotherapy; patients with known infections and patients of recent surgery or trauma, patients having malignancy, pregnant females and lactating mothers were excluded from the study.
A detailed history was elicited from the patient regarding their present complaints associated symptoms alcohol intake, smoking, previous history of hypertension, diabetes mellitus, arthritis, hypothyroidism, any cardiac illnesses and chronic drug intake.

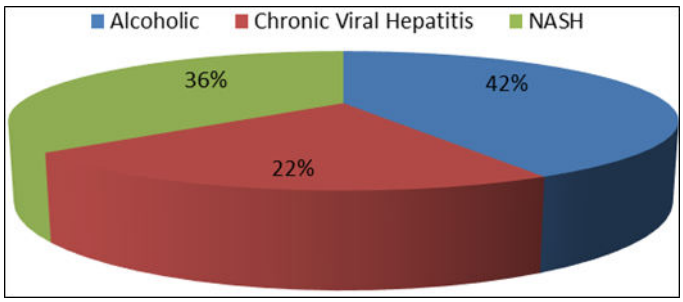
Investigations
On admission routine blood investigations like blood sugar, urea, serum creatinine, liver function test, thyroid profile, lipid profile and PT/INR was sent.
Ultrasonogram abdomen was done and serum uric acid levels were estimated. Waist circumference in males and females was measured. Glycemic and Body mass index were recorded. Serum uric acid level was sent for analysis on the day of admission and was followed up. The reagent for serum uric acid was uricase and for blood glucose titer method was used. Data was collected and analyzed using SPSS version 24.

Statistical analysis: Data so collected was tabulated in an excel sheet, under the guidance of statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 24.00 for windows; SPSS Inc., Chicago, USA). For each assessment point, data were statistically analyzed using one way ANOVA. The level of significance was set at $p < 0.05$.

Results: Table 1 shows the age and gender distribution among the CLD subjects. 4%, 22%, 34% and 40% of the subjects belonged to 18-30, 31-40, 41-50 and 51-60 years respectively. Out of 50 subjects, 38 (76%) were males and 12 (24%) were females.
Table 1: Age distribution among the CLD subjects

Age Group (in years)	**N**	**%**
18-30	2	4
31-40	11	22
41-50	17	34
51-60	20	40
Gender		
Male	38	76
Female	12	24
Total	50	100

Most common etiology of CLD in our study was alcohol (42%) followed by NASH (36%). Chronic viral hepatitis was reported among 22% of the subjects (Graph 1).



Graph 1: Etiology of CLD

Table 2 shows the CTP class among the CLD subjects. CTP class A, B and C was found among 34%, 56% and 10% of the subjects respectively. Mean ± SD uric acid (mg/dl) among the study subjects was 6.69±2.92. Normal uric acid (3.1-5) was revealed among 24% of the subjects while higher uric acid/hyperuricemia was reported

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among 38 (76%) subjects.

Table 2: CTP class and uric acid (mg/dL) among the CLD subjects

CTP Class	**N**	**%**
A	17	34
B	28	56
C	5	10
Uric Acid (mg/dL)		
3.1-5	12	24
5-7	15	30
>7	23	46
Mean ± SD	6.69 ± 2.92	

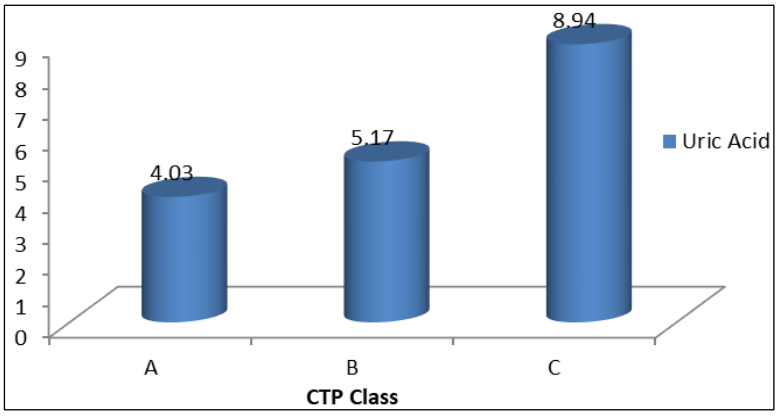
It can be appreciated from the table 3 that as the uric acid level increase, bilirubin also increases with statistically significant difference as p<0.05. The normal range of SGOT to be present in the blood is about 5-40 units per liter of serum. Mean SGOT was 52.68, 59.87 and 118.41 among the subjects having 3.1-5, 5-7 and >7 mg/dl respectively. When SGOT was compared according to the uric acid level using Anova test, it was found to be statistically significant as p<0.05. Also when compared with normal value of SGOT, it was found to be found to significantly high among subjects having uric acid 5-7 and >7mg/dl. The normal range of SGPT to be present in the blood is about 7-56 units per liter of serum. Mean SGPT was 54.39, 59.96 and 119.81 among the subjects having 3.1-5, 5-7 and >7 mg/dl respectively with statistically significant difference.

Table 3: Mean bilirubin among the CLD subjects according to uric acid

Uric Acid (mg/dL)	**Bilirubin**		**p value**
	Mean	**SD**	
3.1-5	2.43	0.92	<0.01*
5-7	2.86	1.07	
>7	5.21	1.97	
Uric Acid (mg/dL)	**SGOT**		**p value**
	Mean	**SD**	
3.1-5	52.68	9.98	<0.01*
5-7	59.87	11.54	
>7	118.41	13.37	
Uric Acid (mg/dL)	**SGPT**		**p value**
	Mean	**SD**	
3.1-5	54.39	12.62	<0.01*
5-7	59.96	14.27	
>7	119.81	15.24	

*: Statistically significant.

Mean uric acid was 4.03, 5.17 and 8.94 among the subjects having CTP class A, B and C respectively. When CTP class was compared according to the uric acid level using Anova test, it was found to be statistically significant as p<0.05 (graph 2).



Graph 2: Mean uric acid according to CTP class

Table 4 shows the correlation of uric acid with various parameters. Pearson correlation analysis revealed significant positive correlation between uric acid and total bilirubin, SGOT, SGPT and CTP Score.

Table 4: Correlation of uric acid with various parameters

Variables	r value	p value
Total Bilirubin	0.59	<0.01*
SGOT	0.43	0.007*
SGPT	0.47	0.004*
CTP Score	0.48	0.004*

*: Statistically significant

Discussion

This study was conducted at Department of Medicine of Subharti medical college Meerut UP
and associated hospital from 2020 to 2021 as a prospective observational study to evaluate the association between serum uric acid levels and chronic liver disease. In this study, we included a total of 50 patients admitted in medicine department with clinical diagnosis of Chronic liver disease.

Prior to our study , many studies done across various countries,had tried to establish the association between serum uric acid levels and chronic liver disease.

Anita Afzali *et al*. in 2010 analyzed the association between serum uric acid levels and chronic liver disease in United States. They found that higher serum uric acid levels were associated with elevated serum alanine aminotransferase (ALT) or g-glutamyl transferase (GGT), two markers of hepatic necroinflammation and were associated with development of cirrhosis [16].

So higher uric acid level was an important risk factor of chronic liver disease.

NAFLD is now recognized worldwide as a major cause of chronic liver disease.

Non-alcoholic fatty liver disease (NAFLD) is a state of intrahepatic fat accumulation, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis.

Majority of the studies had been done among NAFLD patients where there was associated higher uric acid level.

Yong-Jae Lee *et al*. in 2010 found out the association between serum uric acid and non-alcoholic fatty liver disease in Korean adults. Authors concluded that serum uric acid was independently associated with the presence of NAFLD and uric acid might be a useful additional measure in assessing the risk of NAFLD in clinical setting [17].

Later in 2011, Cheol Hwang *et al*. studied 9,019 subjects according to their NAFLD status. Among them, 2,124 (23.6%) subjects met the diagnostic criteria for NAFLD. The mean age and proportion of men was higher in the NAFLD group, and the group showed a high obesity index, more deranged metabolic profile, and elevated results of the liver-function test. In particular, significantly higher serum uric acid levels were observed in the subjects with NAFLD than in those without NAFLD. On the relationship between normal serum uric acid and non-alcoholic fatty liver disease, they suggested that increased serum uric acid concentrations, even within the normal range, were independently associated with presence of NAFLD [18].

Ming-Hsiung Shih *et al*. in 2015 focused on an association between serum uric acid and non-alcoholic fatty liver disease in US population. They showed that the prevalence of NAFLD was higher in participants with higher serum uric acid [19]. However, in their study they did not find an association between NASH and serum uric acid level among patients with NAFLD may be due to the small number of NASH participants.

Indeed, some studies had showed that serum uric acid levels are associated with the progression of chronic liver diseases such as NAFLD and NASH and that hyperuricemia was independently associated with the severity of liver damage among NAFLD patients.

In one such study , Qian Huang *et al*. in 2016 collected 158 adults aged >18 years and diagnosed with biopsy-proven NAFLD for association of the serum uric acid level with liver histology in biopsy proven non-alcoholic fatty liver disease [14].

The differences in liver histology were assessed between hyperuricemic and normal serum uric acid groups with NAFLD to determine the possible risk factors.

In conclusion, hyperuricemia was associated with histologically severe NAFLD. Hyperuricemia was independently associated with greater odds of advanced lobular inflammation of NAFLD.

The results revealed no association between hyperuricemia and advanced fibrosis of NAFLD. The cross-sectional study did not confirm the causal association between hyperuricemia and liver fibrosis. Additional prospective studies are required to provide evidence linking hyperuricemia with liver fibrosis.

Guntur Darmawan *et al*. in 2017 did a meta-analysis on association between serum uric acid and non-alcoholic fatty liver disease. It was concluded that there were two studies done that demonstrated association between serum uric acid levels and NAFLD [13].

More recently, Vathsalyan *et al*. in 2020 evaluated the association between serum uric acid and non-alcoholic

fatty liver disease and its correlation with liver fibrosis as assessed by fibroscan. This study showed significant correlation between serum uric acid and NAFLD [15].

Hence an Increase in serum uric acid levels might serve as a trigger for a physician to screen for NAFLD.

Bobbi Singh M *et al*. in 2019 collected 66 patients suffering from chronic liver disease, out of which 48 (72.7%) were male. Alcohol was the most common cause (69.7%) of CLD followed by chronic hepatitis C (15.2%). They concluded that uric acid was higher in patients with CLD and serum uric acid was higher with higher CTP score which was an oxidative marker for liver damage [2].

Prakash BC *et al*. [12] in 2020 analyzed the relevance of serum uric acid in liver cirrhosis and its correlation with Child Turcotte Pugh, MELD and UKELD score. The study showed a positive correlation between serum uric acid levels and various available scoring systems such as CTP score, MELD and UKELD score. Hence serum uric acid could be used as an alternative prognostic parameter in predicting the severity and prognosis of cirrhosis of liver.

Liver injury is characterized by high blood level of oxidative marker. Uric Acid may be considered as a marker of oxidative stress. The level is found to correlate with higher CTP grade.

Conclusion

Elevated serum UA level might be a risk factor for the incidence of chronic liver disease. Hyperuricemia may act as a surrogate marker for assessing the prognosis of CLD. However, further larger prospective case control studies are needed to show the relationship between serum uric acid and severity of chronic liver disease. If this is confirmed, uric acid can be used as a marker of severity of CLD and can be used in the assessment of prognosis of CLD.

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