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Original Research Article

A study of the prevalence of hyperuricemia as well as its association with non-alcoholic fatty liver disease in three hundred patients at a tertiary care centre in North-East India

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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. Thus, we intended to perform this cross-sectional study to establish the prevalence of hyperuricemia in NAFLD patients and its association with NAFLD in 300 patients at a tertiary care centre in North-East India.
Methods: In this hospital based cross-sectional study, 300 patients presenting in Assam medical college and hospital (AMCH) with diagnosed NAFLD were included during the one year period from July 2015 to June 2016.
Results: Hyperuricemia was observed in 99 cases out of a total of 300 cases of NAFLD (33%), and a statistically 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 ($p<0.001$).

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] Subgroups 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. 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 comprises a wide spectrum of liver damage, ranging from simple benign fatty liver (hepatic steatosis) to NASH, characterized by fatty change with lobular inflammation, hepatocellular injury, and mallory hyaline, progressive fibrosis, and cirrhosis, and has been defined both histologically and clinically.[4]

The prevalence of NAFLD globally is 25.24% with wide geographical variation across the world. Majority of the

studies on NAFLD epidemiology, however, has been from the United States of America (USA) and North America with a NAFLD prevalence rate of 21-24.7%. In Asia, it varies from 12.5-38% in Chinese Mainland, 23-26% in Japan, 27% in Korea, 12-51% in Taiwan, 28% in Hong Kong, 9-32% in India and 5-30% in other areas of South Asia and far East (Srilanka, Malaysia, Srilanka and Indonesia).[5] The prevalence of NAFLD increases significantly, to 57.5% to 74%, in obese individuals.[6] In the USA it has been estimated that steatosis affects about 70% of the obese population, whereas NASH is found in 19% of these obese individuals.[7,8] Due to this risk of progression to severe liver disease through the consequences of its fibro-inflammatory risk, NAFLD has been predicted to be the major cause of liver transplantation in 2020 (Charlton, 2004) stressing great need for the early detection of this disease.[9]

In recent years, an association between elevated serum uric acid concentrations and NAFLD has been reported. Some studies have concluded that hyperuricemia is an independent risk factor for NAFLD, and is even related to its histologic severity. However, no study from the North-Eastern part of the country has yet been done to determine the association of serum uric acid levels with NAFLD. Thus, we intended to perform a cross-sectional study to examine the prevalence of increased uric acid levels in patients with NAFLD and to study the association if any, between increased serum uric acid levels and NAFLD in patients presenting to 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 sample size of 300 patients was taken up for study from the inclusion criteria as mentioned below and data was collected using a pretested proforma meeting the objectives of the study.

Inclusion criteria

It 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/m^2), and females with polycystic ovarian disease (PCOD).

Exclusion criteria

It consisted of 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 were 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[10]

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.

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 on ultrasound was made on the basis of the increased echogenicity of the liver parenchyma.[11]

Statistical methods

Chi-square test (X_2) and student paired t-test (two tail type 3) were used to compare the baseline patient characteristics, and to illustrate the significance of the association between serum uric acid levels and NAFLD.

RESULTS

Table 1 shows that the study group comprised of 300 patients with a mean age of 47.31±12.26 years, minimum age of 17 years and maximum age of 82 years. In the study group, majority of the patients (36.67%) were in the age group of 40-49 years (n=110).

Table 1: Age distribution in NAFLD patients.

Age group (in years)	Number (n)	Percentage (%)
<20	1	0.33
20-29	18	6.00
30-39	60	20.00
40-49	110	36.67
50-59	59	19.67
60-69	33	11.00
≥70	19	6.33
Total	300	100.00
Mean±SD (years)	47.31±12.26	

In the study group, 41.33% were males (n=124) and 58.67% were females (n=176). A female predominance was noted as seen in Table 2.

Table 3 shows the BMI distribution in NAFLD patients. 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 2: Sex distribution of NAFLD patients.

Sex	Number (n)	Percentage (%)	Ratio (Male:female)
Male	124	41.33	1:1.42
Female	176	58.67	
Total	300	100.00	

Table 3: Body mass index (BMI) distribution in NAFLD patients.

BMI (kg/m^2)		Number (n)	Percentage (%)
Underweight to normal	<25	0	0.00
Overweight	25-29.9	237	79.00
Obese category I	30-34.9	63	21.00
Obese category II	35-39.9	0	0.00
Severe obesity	>40	0	0.00
Total		300	100.00

The prevalence of diabetes in NAFLD cases was quite evident as seen in Table 4 with 74.33% cases (n=223) being cases of type 2 diabetes, and the remaining 25.67% cases (n=77) being non-diabetic patients of NAFLD.

Table 4: Diabetic/non-diabetic patients among NAFLD population.

Diabetic/non diabetic	Number (n)	Percentage (%)
Diabetic	223	74.33
Non diabetic	77	25.67
Total	300	100.00

As is evident from Table 5, hyperuricemia was seen in 38 out of 124 male patients of NAFLD (30.65%), and in 61 (34.66%) out of a total of 176 female NAFLD patients.

Table 5: Serum uric acid in males.

Parameter	Uric acid levels in males (mg/dl)		Uric acid levels in females (mg/dl)	
	3.4-7.2	**>7.2**	**2.4-6.1**	**>6.1**
Number of patients (n)	86	38	115	61
Percentage (%)	69.35	30.65	65.34	34.66

Table 6 shows the association of hyperuricemia with various parameters in male NAFLD patients. Elevated uric acid levels were seen to be significantly associated with increasing age and BMI (p value <0.05 for both) as well as with type 2 diabetes (p value <0.05).

Table 7 shows the association of hyperuricemia with various parameters in female 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).

Table 6: Clinical characteristics of NAFLD with and without hyperuricemia in males.

Clinical characteristics	Hyperuricemia		P value
	With (n=38)	**Without (n=86)**	
Age, mean±SD (years)	51.18±9.95	43.70±9.25	0.00019
BMI, mean±SD (kg/m^2)	30.03±1.41	27.79±1.67	<0.001
Diabetes mellitus, n (%)	37 (97.37)	70 (81.39)	0.01712

Table 7: Clinical characteristics of NAFLD with and without hyperuricemia in females.

Clinical characteristics	Hyperuricemia		P value
	With (n=61)	**Without (n=115)**	
Age, mean ±SD (years)	57.72±12.43	43.21±11.28	<0.001
BMI, mean±SD (kg/m^2)	29.85±1.77	27.42±1.47	<0.001
Diabetes mellitus, n (%)	53 (86.89)	63 (54.78)	0.00019

Table 8 shows the relationship between NAFLD and increased uric acid levels; hyperuricemia was observed in 99 cases out of a total of 300 cases of NAFLD (33%), with a statistically significant association between the two (p value <0.001).

Table 8: Association between NAFLD and serum uric acid levels.

Parameter	Total number of cases	Hyperuricemia		
		With n (%)	**Without n (%)**	**P value**
NAFLD	300	99 (33)	201 (67)	<0.001

DISCUSSION

NAFLD is now recognized worldwide as an important cause of chronic liver disease (CLD) and the disease burden is increasing rapidly. The present study was carried out in three hundred cases of NAFLD to establish the prevalence of hyperuricemia in NAFLD as well as to study the association of hyperuricemia and NAFLD as diagnosed 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 to a cross-sectional study by Kojima et al in 2003, in which 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.[11] Azharuddin et al in 2016 studied 144 patients of NAFLD with the mean age being 48.82±11.21 years with maximum patients in the age group of 40-50 years and Majumdar et al in 2016 also found maximum patients in the age group of 35-49 years (79 patients) which comprised 44.9% of the study group.[12,13]

In our study, there were a total of 176 females and 124 males with a female:male ratio of 1.42:1. There was a female predominance in all age groups. Studies such as those done by Kalra et al showed prevalence of the disease was found to be higher in females (60%) than in males (54.3%).[14] A female predominance was also seen in the study done by Majumdar et al in 2016 in a rural Haryana population.[13]

In our study, majority of the patients i.e. 79% (n=237) were in the overweight category (BMI=25-29.9) while 21% (n=63) were in the obese category I (BMI=30-34.9). The mean BMI overall was 28.35±1.93 kg/m^2 while it was 28.48±1.90 kg/m^2 and 28.26±1.96 kg/m^2 in males and females respectively. In a recent consensus meeting in Delhi, it was concluded that central or abdominal obesity is more commonly associated with insulin resistance and has been observed in 80-90% of Indian patients with NAFLD.[15-17]

In our study, it was observed that out of the 300 patients enrolled in the study, 223 were diagnosed cases of type 2 diabetes mellitus which comprised 74.33% of the study group while the remaining 77 patients had no history of diabetes. Similar NAFLD and its clinical correlates in a population of patients with type 2 diabetes mellitus (T2DM) was seen by Forlani et al and Mhetre et al in 2016 where NAFLD was associated with 47.5% of T2DM patients.[18,19]

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 a 124 male patients and 61 (20.33%) out of a 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%.[20] Petta et al observed that about 20% of the patients in his study group had hyperuricemia, which was independently associated with younger age and lobular inflammation.[21]

The prevalence rates of NAFLD determined by abdominal ultrasound examination in a study done by Cai et al and hyperuricemia were 43.9% and 8.4%, respectively with the NAFLD patients having significantly higher serum uric acid levels than those without NAFLD (p value <0.001).[22] 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). Prevalence of hyperuricemia was 53.2% in a 2016 study done by Huang et al and in a study conducted by Azharuddin et al 2016, it was seen that mean SUA were significantly higher in patients with NAFLD (p value <0.001).[12]

The proportion of NAFLD was 29.4% (33.9% in men and 23.5% in women) in a study done by Valiyakath et al in 2015 and in multivariate logistic regression analysis, an independent association between serum uric acid concentrations and the presence of NAFLD was observed. A similar association of hyperuricemia and NAFLD was shown in the studies done by Lee et al and Afzali et al in 2010.[23,24]

In our study, the male hyperuricemics (n=38) had a mean uric acid level of 8.33±0.83 mg/dl as compared to 5.16±1.19 mg/dl in male patients with normal uric acid levels (n=86) resulting in a significant association (p value <0.001). The elevated uric acid levels in male patients were also significantly associated with increasing age and BMI (p value <0.05 for both). On observing the females with elevated uric acid levels (n=61), the mean uric acid level was 7.73±1.13 mg/dl as compared to 4.75±0.96 mg/dl in non-hyperuricemic females (n=115). This leads to a significant association (p value <0.01). On observing the association of hyperuricemia with increasing age and BMI, a significant association was seen (p value <0.001 for both).

However, this study was not without limitations. Firstly, the study was a single centered, cross sectional and observational hospital based study and was done within a short time period of one year and comprised of a limited number of cases. Therefore, because of its cross-sectional design, a causal relationship between SUA and NAFLD could not be identified. Secondly, although 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%. Thirdly, the amount of alcohol intake and exercise was measured by a questionnaire so that it is likely that this method introduced a measurement bias.

CONCLUSION

Our findings demonstrated an independent association between NAFLD and increased SUA levels 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 intra-cellularly, uric acid may have a pro-inflammatory and pro-oxidant role.

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.

However, it may be potentially useful to investigate longitudinally whether hyperuricemia is a cause or a marker for disease outcomes in NAFLD. If this is confirmed, further consideration can be given to measures that reduce the SUA levels as a means of preventing NAFLD in patients with elevated levels of uric acid.

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