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A study of serum uric acid in nonalcoholic fatty liver disease patients

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Abstract

Introduction: Nonalcoholic fatty liver disease (NAFLD) is a common form of chronic liver disease and serum uric acid is observed to be significantly elevated in NAFLD patients. Increased uric acid is associated with the metabolic syndrome, conditions linked to oxidative stress and insulin resistance. Nonalcoholic fatty liver disease is now considered a hepatic manifestation of insulin resistance. However association between uric acid and NAFLD is known very little only.

Aim: This study is aimed at the correlation between high serum uric acid levels and nonalcoholic fatty liver disease.

Material and methods: This was an observational cross sectional study conducted in patients admitted to the General Medicine wards and medical OPD with clinical features suggestive of NAFLD. All patients with evidence of NAFLD in clinical features and imaging were taken up for the study based on strict inclusion and exclusion criteria and their serum uric acid was done. Patients details regarding various risk factors and clinical features were recorded on a well thought out and carefully prepared proforma. The data was analyzed and the results were compared with other available similar studies.

Results: The average age of patients in this study was 53.84 years. Of the 50 patients studied, 48 % were males and 52 % were females. Most of the patients were above 40 years of age. Hyperuricemia was found to be one of the most important risk factor. NAFLD patients with hyperuricaemia have considerable risk of progression of their fatty liver disease severity. Patients with fatty liver and its association with increased serum uric acid was analyzed. These results were compared with various other studies. The results were comparable between these studies.

Conclusion: Uric acid is an old molecule with many new applications and it has also been studied in various metabolic diseases, cardiovascular diseases and chronic kidney disease. In this study it has been found that increased serum uric acid has a significant correlation with NAFLD, obesity, hypertension, increased body mass index (BMI), triglyceride and increased cholesterol levels in blood.

Keywords: Serum uric acid, Nonalcoholic fatty liver disease.

Introduction

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of conditions from simple steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis. It has become one of the most prevalent liver diseases in Western countries, affecting 20%–30% of the general population [1], [2] . NAFLD is an emerging problem in the Asia-Pacific region and the prevalence is likely to increase in the future [3], [4]. Simple steatosis is generally a benign condition; however, NASH can progress to cirrhosis and liver failure [5] and the 5-year survival rate for individuals diagnosed with NASH is estimated to be only 67% [6].

Identifying risk factors is essential for the prevention of NAFLD. The development of NAFLD is a multifaceted cascade of physiologic and biochemical events, including genetic [7], environmental [8], metabolic [9] and stress-related factors [10]; the exact risk factors for NAFLD have not been fully clarified. Recent studies showed that NAFLD is closely associated with obesity, hypertension, dyslipidemia and glucose intolerance, a cluster of metabolic disorders that is now recognized as metabolic syndrome [11], [12]. For this reason, NAFLD has been considered as the hepatic manifestation of metabolic syndrome [12].

Uric acid is the end product of purine metabolism and the serum uric acid (SUA) level is maintained by the balance between uric acid production and excretion [13]. Previously, more and more studies suggested that the SUA levels were significantly elevated in chronic metabolic diseases, such as cardiovascular disease [14], type 2 diabetes mellitus [15] and metabolic syndrome [16].

However, the relationship between NAFLD and SUA has not been clarified. A recent cross-sectional study demonstrated that SUA levels were significantly elevated in NAFLD patients and that the prevalence rate of NAFLD increases as SUA levels increase [17]. These results suggested that elevated SUA levels may be associated with NAFLD [17]. However, whether this association is causal, a bystander, or a consequence of NAFLD remains under debate.

Aim of the study

1.To estimate serum uric acid levels in nonalcoholic fatty liver disease patients.
2.To assess the prevalence of hyperuricaemia in nonalcoholic fatty liver disease patients.

Materials and Methods

This was an observational cross sectional study conducted in patients admitted to the General Medicine wards and medical OPD with clinical features suggestive of NAFLD. All patients with evidence of NAFLD in clinical features and imaging were taken up for the study based on strict inclusion and exclusion criteria and their serum uric acid was done. The study includes a standardized questionnaire and examination of the patients included in this study. A total number of 50 patients who are all diagnosed to have fatty liver were included in this study, out of which 24 were males and 26 were females.

Inclusion criteria

All patients more than 18 years of age who were diagnosed to have NAFLD were included in the study.

Exclusion criteria

Age less than 18 yrs, gout and other rheumatologic diseases, diabetes mellitus, chronic alcoholism, known case of alcoholic liver disease, positive test for hepatitis B antigens or hepatitis C antibodies, history of drug intake, malignancy, respiratory disease, renal disease, subjects on hepatotoxic drugs.

Methods

All patients having NAFLD were included in 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 illness and chronic drug intake and thorough physical examination was done using standardized protocol.

On admission routine blood investigations like FBS, serum urea, serum creatinine, SGOT, SGPT, lipid profile, ultrasonogram and serum uric acid levels were done. Body mass index was calculated as weight in kg/ height in m2. Hyperuricaemia was defined according to sex-specific serum uric acid levels: serum uric acid > 7.0 mg/dL for men and serum uric acid >6.0 mg/dL for women. The diagnosis of NAFLD was based on abdominal ultrasound without including alcohol consumption, viral or autoimmune liver disease. The presence and severity of hepatic steatosis was classified into three groups, grade 1 (mild), grade 2 (moderate) and grade 3 (severe) according to the hyperechogenicity of liver tissue, difference of echogenicity between the liver and diaphragm and visibility of vascular structures. Liver with any degree of hepatic steatosis was considered fatty in the present study. Patients diagnosed as NAFLD were divided into 4 groups according to their serum uric acid levels which were defined as: 3.0-5 mg/dl, 5.1-7.0 mg/dl, 7.1-9.0 mg/dl >9.0 mg/dl respectively.

Statistical analysis

The data was tabulated and analyzed with spss17.0 statistical software. Mean ±SD, p value by chi square test, range and percentages were calculated. One way Anova, Post hoc and student's t test for data and chi square test for consolidation of tables was used. A p value of <0.05 was taken as significant relationship.

Results and Observations

It was an observational cross sectional study which was conducted on 50 NAFLD patients of which males and females were almost equal in number i.e. 24 males (48%) and 26 females (52%). Mean age of our study population was 53.84±14.2years (table 1). Mean age in males was 48.33±13.4 years and in females was 58.92±13.2 years (table 2). Mean serum uric acid in our study was 6.32±1.39mg/dl, in males was 6.70±1.37 mg/dl and in females was 5.96±1.35 mg/dl(table3).Males had higher serum uric acid levels as compared to females but p value was 0.226 which was not significant. In our study, 62% of the patients were hypertensive. Hypertension was significantly associated with increased serum uric acid levels as p value was less than 0.001 (table 4).

Table 1 Age distribution

Age group (years)	No. of cases	%age
21-30	5	10.0
31-40	4	8.0
41-50	10	20.0
51-60	18	36.0
61-70	9	18.0
71-80	2	4.0
81-90	2	4.0
Total	50	100.0
mean age	53.84±14.20	

Table 2 Age wise distribution according to sex

Age group (years)	Sex				Total	
	Male		Female			
	No.	%	No.	%	No.	%
21-30	5	20.83	0	0.00	5	10.00
31-40	2	8.33	2	7.69	4	8.00
41-50	3	12.50	7	26.92	10	20.00
51-60	10	41.67	8	30.77	18	36.00
61-70	4	16.67	5	19.23	9	18.00
71-80	0	0.00	2	7.69	2	4.00
81-90	0	0.00	2	7.69	2	4.00
Total	24	100.00	26	100.00	50	100.00
MEAN AGE	48.33±13.40		58.92±13.2		53.84±14.20	

Table 3 Mean SUA According to sex

Sex	Serum uric acid(mg/dl)	
	Mean	Standard deviation
Male	6.70	1.37
Female	5.96	1.35
Total	6.32	1.39

Table 4 Distribution of hypertensives and non hypertensives according to SUA levels

Serum uric acid(mg/dl)	Hypertension				Total	
	Yes (n=31)		No (n=19)			
	No.	%	No.	%	No.	%
3.1-5.0	1	3.23	11	57.89	12	24.00
5.1-7.0	9	29.03	6	31.58	15	30.00
7.1-9.0	19	61.29	2	10.53	21	42.00
>9.0	2	6.45	0	0.00	2	4.00
p value	<0.001 (significant)					

Obesity constituted 52% of the study population in our study and there was significant association between increased serum uric acid levels and obesity as p value was <0.001(table 5).

Table 5 Distribution of obese and non obese according to SUA levels

Serum uric acid (mg/dl)	Obesity				Total	
	Yes (n=26)		No (n=24)			
	No.	%	No.	%	No.	%
3.1-5.0	0	0.00	12	50.00	12	24.00
5.1-7.0	5	19.23	10	41.67	15	30.00
7.1-9.0	19	73.08	2	8.33	21	42.00
>9.0	2	7.69	0	0.00	2	4.00
p value	<0.001 (significant)					

In this study the increased BMI was significantly associated with higher serum uric acid levels as p value was <0.001 (table 6). In this studied population significant association was found between increased serum cholesterol and triglyceride levels with increased serum uric acid levels as p value was <0.001 (table 7& 8)

Table 6 Mean body mass index in various SUA levels

Serum uric acid (mg/dl)	No. of cases	Mean BMI (kg/m^2)	Standard deviation
3.1-5.0	12	23.80	1.00
5.1-7.0	15	25.18	1.75
7.1-9.0	21	26.41	1.70
>9.0	2	29.50	0.70
p value	<0.001 (significant)		

Table 7 Mean serum cholesterol in various SUA levels

Serum uric acid (mg/dl)	No. of cases	Mean serum cholesterol (mg/dl)	Standard deviation
3.1-5.0	12	126.08	18.64
5.1-7.0	15	157.46	20.27
7.1-9.0	21	208.47	17.89
>9.0	2	235.00	1.41
p value	<0.001 (significant)		

Table 8 Mean serum triglyceride in various SUA levels

Serum uric acid (mg/dl)	No. of cases	Mean serum triglyceride (mg/dl)	Standard deviation
3.1-5.0	12	132.50	17.90
5.1-7.0	15	149.53	18.22
7.1-9.0	21	208.38	27.47
>9.0	2	224.00	5.66
p value	<0.001 (significant)		

There was no association between serum LDL levels and serum uric acid levels as p value was 0.685(table 9).

Table 9 Mean serum LDL in various SUA levels

Serum uric acid (mg/dl)	No. of cases	Mean serum LDL(mg/dl)	Standard deviation
3.1-5.0	12	135.91	20.3
5.1-7.0	15	143.06	13.9
7.1-9.0	21	139.52	16.16
>9.0	2	132.00	39.59
p value	0.685 (not significant)		

In this study serum HDL levels were inversely associated with increased serum uric acid levels as p value was 0.028 (table 10). In this study serum bilirubin levels showed significant association with increasing serum uric acid levels as p value was <0.001 (table 11).

Table 10 Mean serum HDL in various SUA levels

Serum uric acid (mg/dl)	No. of cases	Mean serum HDL(mg/dl)	Standard deviation
3.1-5.0	12	57.00	5.44
5.1-7.0	15	51.86	5.89
7.1-9.0	21	50.00	7.07
>9.0	2	47.00	14.10
p value	0.028 (significant)		

Table 11 Mean serum billirubin in various SUA levels

Serum uric acid (mg/dl)	No. of cases	Mean serum bilirubin (mg/dl)	Standard deviation
3.1-5.0	12	2.53	0.47
5.1-7.0	15	2.91	0.7
7.1-9.0	21	4.80	0.92
>9.0	2	4.70	1.06
p value	<0.001 (significant)		

The present study showed that that there was association between increased serum uric acid and increased FBS levels as p value was 0.011 (table 12).

Table 12 Mean FBS in various SUA levels

Serum uric acid (mg/dl)	No. of cases	Mean FBS (mg/dl)	Standard deviation
3.1-5.0	12	91.33	8.39
5.1-7.0	15	102.46	9.70
7.1-9.0	21	98.50	4.00
>9.0	2	94.00	28.02
p value	0.011 (significant)		

This study showed that there was significant association between increased serum uric acid levels and fatty liver disease and its severity as p value was <0.001(table 13).The overall prevalence of hyperuricaemia in the study was 52% (table 14) in males 54.2% and in females 50% (table 15).

Table 13 Distribution of fatty liver according to SUA levels

Serum uric acid (mg/dl)	Fatty liver						Total	
	I		II		III			
	No.	%	No.	%	No.	%	No.	%
3.1-5.0	10	76.92	2	9.52	0	0.00	12	24.00
5.1-7.0	3	23.08	10	47.62	2	12.50	15	30.00
7.1-9.0	0	0.00	9	42.86	12	75.00	21	42.00
>9.0	0	0.00	0	0.00	2	12.50	2	4.00
Total	13	100.00	21	100.00	16	100.00	50	100.00
p value	<0.001(significant)							

Table 14 Prevalence of Hyperuricemia

Hyperuricemia	No. of cases	%age
Present	26	52.0
Absent	24	48.0

Table 15 Prevalence of hyperuricemia according to sex

Hyperuricemia	Sex			
	Male		Female	
	No.	%	No.	%
Present	13	54.2	13	50.0
Absent	11	45.8	13	50.0

In this study, hyperuricaemia was significantly associated with severity of fatty liver disease as p value was less than 0.001(table 16).

Table 16 Percentage of hyperuricemic patients according to severity of NAFLD

Hyperuricemia	Fatty liver						Total	
	I		II		III			
	No.	%	No.	%	No.	%	No.	%
Present	0	0.00	11	52.38	15	93.75	26	52.00
Absent	13	100.00	10	47.62	1	6.25	24	48.00
Total	13	100.00	21	100.00	16	100.00	50	100.00
p value	<0.001(significant)							

Discussion

Out of the 50 patients studied, the mean Serum uric acid in the total population is 6.32±1.39 mg/dl, of which men had higher mean Serum uric acid level when compared to female. But there was no statistical significance between these two groups. This was in accordance to the studies done by Xu et al[18].

The mean age in the study group was 53.84±14.2 years. Mean age in males was 48.33±13.4 years and in females was 58.92±13.2 years. Women had higher mean age compared to men. The mean age of onset of liver disease is higher in female compared to male.

In this study hypertension[19] and obesity[20] were significantly associated with increased serum uric acid levels which were in accordance to previous studies.Hyperbilirubinemia[21], Hypercholesterolemia[22], Hypertriglyceridemia[23] and BMI[24] were significantly associated with increased serum uric acid levels. Body mass index showed statistically significant association with serum uric acid levels. South Asian people are more prone for development of cardiovascular disease even in the presence of lower BMI. This indicates that people with higher BMI have still more increase in the cardiovascular risk. Studies done in this association of BMI with uric acid showed similar proven results. In our study we observed that increased serum uric acid levels were directly associated with fatty liver disease and its severity. One possible explanation for the relationship between serum uric acid and NAFLD is that the observations are simply confounded by the shared background of metabolic syndrome. Supporting this theory are the observations that hyperinsulinemia can induce hyperuricaemia by decreasing urinary excretion of uric acid[25] and that hyperuricemia can result from the oxidative stress seen in metabolic syndrome.[26]

Uric acid has been shown to exert pro-inflammatory and pro-oxidant effects both in adipose tissue[27,28] and in other cell lines such as vascular smooth muscle cells [29,30] where uric acid has been shown to act as an intracellular pro-oxidant activating the mitogen activated protein kinase pathway and nuclear factor κ-B. The overall prevalence of hyperuricaemia in our study was 52%.Hyperuricaemia was significantly associated with severity of fatty liver disease. Similar results were obtained in a study done by Jaruvongvanich et al[31].This shows that people with fatty liver and hyperuricemia in future may progress to the advanced liver disease, cirrhosis which is correlated well with the laboratory values of liver function tests.

Conclusion

Uric acid is an old molecule with many new applications and it has also been studied in various metabolic diseases, cardiovascular diseases and chronic kidney disease. In this cross sectional observational study it has been observed that increased serum uric acid levels are well associated with NAFLD due to oxidative stress and inflammatory actions. It was concluded that increased serum uric acid is associated with NAFLD and also has significant association with obesity, hypertension, increased BMI, triglyceride and increased cholesterol levels in blood. This study also clearly indicates that NAFLD patients with hyperuricaemia have considerable risk of progression of their fatty liver disease severity. Because of its association with BMI, waist circumference and hypercholesterolemia, hyperuricemia may be considered as one the risk factor for metabolic syndrome.

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