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ASSOCIATION OF HIGH SERUM URIC ACID IN CHRONIC LIVER DISEASE

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A R T I C L E I N F O

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A B S T R A C T

Back ground: Nonalcoholic fatty liver disease (NAFLD) is a common form of chronicliver 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. Non-alcoholic fatty liver disease(NAFLD) is now considered a hepatic manifestation of insulin resistance. However association between uric acid and NAFLD known very little only. This study is aimed at the correlation between high serum uric acid level and chronic liver disease. **Keywords:** *Inflammation, insulin resistance, non-alcoholic fatty liver disease, uric acid.***Materials and methods:** This was a prospective observation study conducted in patients admitted to the General Medicine wards and medical gastroenterology ward with clinical features suggestive of chronic liver disease. All patients with evidence of chronic liver disease in clinical features and/or imaging were taken up for the study based on strict inclusion and exclusion criteria. Patients' details regarding various risk factors and clinical features were recorded on a well thought out and carefully prepared proforma. The data was analysed and the results were compared with other available similar studies. **Results:** The average age of patients in this study was 46.81 years. Of the 100 patients studied, 75 % were males and 25 % were females. Most of the patients were above 40 years of age. Hyperuricemia was found to be one of the most important risk factor followed by hyperlipidemia and obesity. Smoking was found have no correlation in this study. Patients with cirrhosis and fatty liver and its association with hyperuricemia analysed. 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 uric acid has a significant correlation with BMI, waist circumference, hypercholesterolemia and nonalcoholic fatty liver disease.

INTRODUCTION

In higher animals and humans the serum uric acid is an end product ofpurine metabolism, excreted mainly through kidneys. Increased serum uric acidlevels was thought to be the main reason for arthritis due to crystal deposition injoints, renal stones and other vascular events. More recently, increased levels of serum uric acid levels also involved in the future development of hypertension, cardiovascular disease, kidney disease and metabolic syndrome (Sanyal, 2005; Moucari *et al.,* 2008 and Edwards, 2009). Although increased serum uric acid levels are involved in the development of many diseases the following mechanisms included as a cause, they are dysfunction of endothelium, resistance to insulin, systemic inflammation and oxidative stress. Several biological studies shown that increased serum uric acid level have been found to correlate directly with the level of tissue injury. Compared to the serum levels of uric acid, tissue levels of uric acid has better prediction of tissue injury. So serum uric acid may be considered as an indicator of tissue injury Recent studies on serum uric acid have shown an increased serum uric acid levels associated with the development of steatosis of liver in the patients who had Non-Alcoholic fatty Liver Disease (NAFLD) after adjustment for various features of metabolic syndrome. It is proposed that the role of increased uric acid levels in the pathogenesis of liver disease thought to be due to its pro-inflammatory effects, for example, increased levels of uric acid is considered as an important marker in the pathogenesis of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steato hepatitis (NASH) (CDCP, 1996; Choi and Ford, 2007 and Ioannou *et al.,* 2003). Addition to this, hyperuricemia involved in the progressive development of hepatitis C virus related disease and liver diseases due to excessive consumption of alcohol (Feig *et al.,* 2008). This strongly suggests that increased uric acid levels, strongly reflects and even causes an increased oxidative stress, resistance to insulin and inflammation in the systemic circulation. This become one of the main risk factors for future development of cirrhosis of liver or hepatic inflammation due to necrosis both in alcoholic and non-alcoholic Oxidative stress in liver mainly caused by the mitochondrial dysfunction, and also by proinflammatory cytokines like tumor necrosis factor alpha (TNF) are thought to play a very important role in the progression of liver cell

damage in cases of nonalcoholic fatty liver disease NAFLD not only directly leads to the development of liver failure and hepatocellular carcinoma, but also is involved in the future development of type 2 diabetes and cardiovascular diseases due to atherosclerosis. NAFLD is complex disease and nowadays it is challenging for the human health. In chronic liver disease due to various causes uric acid levels are found to be increased .Most of the people with nonalcoholic fatty liver disease, the increased uric acid levels are implicated as an important etiological risk factor. Also increased uric acid level has a known effect on alcohol metabolism, hyperuricemia also be found in patients with alcoholic liver disease. Recent cross-sectional studies showed that increased serum uric acid levels are reasonably increased in NAFLD and also the prevalence rate of NAFLD increases as the serum uric acid levels increases (NHANES 2001-2002; Ioannou *et al.,* 2005 and Ioannou *et al.,* 2006). These results concluded that elevated serum levels of uric acid may be associated with the development of nonalcoholic fatty liver disease. However, whether this association of serum uric acid and liver disease is causal, a bystander, or a consequence of NAFLD still remains under debate.

Aim of the Study

- To assess the prevalence of hyperuricemia in nonalcoholic patients with cirrhosis liver and fatty liver
- To study the association of uric acid and various risk factors
- To study the usefulness of serum uric acid as an prognostic marker in chronic liver disease

MATERIALS AND METHODS

Study Design: This is a prospective study conducted on a sample south Indian population admitted in department of medicine and department ofgastroenterology during the period of 2013 and 2014. The study includes astandardized questionnaire and examination based on this patients wereincluded in this study. A total number of 100 patients who are all diagnosed to have fatty liver and cirrhosis are included in this study. Patients with priorhistory of alcoholic liver disease, chronic kidney disease, arthritis, cardiovascular disease and diabetes mellitus, hypothyroidism are excluded.The total number of patients included in this study was 100 out of which 75 are males and 25 are females

Inclusion Criteria: Age of the patients between 30 years to 60 years without the prior history of alcoholism, diabetes mellitus, kidney disease, hypothyroidism, drug intake and cardiac disease

Exclusion Criteria: 1. Age less than 30 years and more than 60 years, 2. Gout 3. Chronic alcoholics, 4. Known case of alcoholic liver disease, 5. Chronic kidney disease, 6. Hypothyroidism, 7. Drug intake, 8. Diabetes mellitus, 9. Cardiac disease, 10. Obesity.

METHODS

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.

On admission routine blood investigations like blood sugar, urea, serum creatinine, liver function test, thyroid profile, lipid profile, ultrasonogram and serum uric acid levels were estimated. Waist circumference in males and females measured. Diabetes was defined as fasting blood sugar>126 mg % and post prandial blood sugar >200 mgs%. Body mass index was calculated as weight in kg/ height in m2. Serum uric acid levels also sent for analysis on the day of admission. The reagent for serum uric acid isuricase and for blood glucose trider method is used.

Statistical Analysis: Data analysis was done and the subjects were divided in to twogroups. One group with ultrasonagram findings of fatty liver and another group with the findings of cirrhosis of liver. Serum uric acid levels in boththe groups are analysed with age and sexUsing the SPSS 20 and sigma stat 3.5 version software, means,standard deviations, range, frequencies, percentages, chi-square and 'p'values were calculated. One way ANONA and student's t test for data andchi square test for consolidation of tables used. A 'p' value of < 0.05 wastaken as significant relationship.

Results and Observations: The study population has 100 patient in the age group of 30 years to 60 years. The mean age of total population is 46.81. The mean age for male is 47.52. The mean age for female is 44.68

Age Distribution in Study Population

The mean age of the total population was 46.81 years. The mean age of malewas 47.52years and the mean age of female was 44.68. The mean age for male is higher than female (table 1). The studied population had 75% of males and 25% of females. The studied population showed among the 100 patients 42 persons had hyperuricemia in the average of 7 to 9. The mean uric acid level is 6.73 (Table 2).

Mean uric level in the studied population was 6.73. Men had relatively higher uric acid levels when compared to women. P value is 0.002 which is significant in this study. Mean uric acid level in male was 6.93 and mean uric acid in female was 6.11. In this studied population patients in the older age group had higher uric acid levels compared to the younger patients. But the P value is 0.792 which showed no significance (Table 3).

In this studied population smoking does not correlated with hyperuricemia. In this studied population hyper bilirubinemia associated with hyperuricemia which is significant. P value is <0.001 (Table 4-7)

In this studied population increased SGOT levels associated with hyperuricemia which is significant. P value is <0.001 (Table 8). In this studied population increased SGPT levels associated with hyperuricemia which is significant. P value is <0.001 (Table 9). In this studied population increased alkaline phosphatase levels associated with hyperuricemia which is significant. P value is <0.001 (Table 10).

In this studied group blood sugar values not correlated with uric acid levels. P value not significant. value is 0.148 (Table 11). In this studied population blood urea levels not correlated well with the uric acid levels. P value not significant (P value 0.094) (Table 12). In this studied group serum creatinine level not correlated with serum uricacid levels. P value 0.093 not significant.

Table 1 Age group of sample population

Age	Male	Female	Total
<30	1	4	5
31 - 40	18	6	34
41 -50	28	6	34
51-60	28	9	37
TOTAL	75	25	10

Table 2 Level of uric acid in different sex of sample population

URICACID Level	MALE	FEMALE	TOTAL
3.1 to 5.0	16	8	24
5.0 to 7.0	17	9	26
7.0 to 9.0	34	8	42
>9.0	8	0	8
TOTAL	75	25	

p value - .002 significant

Table 3 Level of uric acid in different age group of sample population

URIC ACID LEVEL	<30	31 to 40	41 to 50	>50
3.0 to 5.0	3	7	8	6
5.0 to 7.0	0	8	9	9
7.0 to 9.0	1	8	16	17
>9.0	1	1	1	5
TOTAL	5	24	34	37

p value - 0.792 significant

Table 4 Level of uric acid and BMI in different age group of sample population

URIC ACID	22 to 23	23.1 to 24	24.1 to 25	>25
3.0 to 5.0	6	13	4	1
5.0 to 7.0	2	8	9	7
7.0 to 9.0	0	2	16	24
>9.0	0	0	0	8
TOTAL	8	23	29	40

P Value - .009 **SIGNIFICANT**

Table 5 Level of uric acid in sample population

URIC ACID	No OF CASES	YES	NO
3.0 to 5.0	24	4	20
5.1 to 7.0	26	9	17
7.1 to 9.0	42	0	42
>9	8	0	8
TOTAL	100		

Table7 Level of Bilirubin in sample population

BILIRUBIN	NO OF CASES	MEAN	STD DEV
3.0 to 5,0	24	2.492	0.836
5.1to 7.0	26	2.788	1.493
7.1 to 9.0	42	5.188	1.659
>9	8	4,425	2.241
TOTAL	100	P VALUE < 0,001	

Table 6 Level of uric acid and waist in sample population

URIC ACID	75to 80	81 to 85	86 to 90	91 to 95	96 to 100	101 to 110
3.1 to 5.0	11	4	3	4	2	0
5.1 to 7.0	3	7	6	6	4	0
7.1 to 9.0	0	0	5	5	12	19
>9.0	1	0	1	3	1	3
TOTAL	100	P value = 0.012 **SIGNIFICANT**				

Table 8 Level of SGOT in sample population

URIC ACID	NO OF CASES	MEAN	STD DEV
3.1 to 5.0	24	50.25	46.832
5.1 to 7.0	26	58.462	23.261
7.0 to 9.0	42	103.905	70.162
>9	8	141.5	158.98
TOTAL	100	P VALUE <0.001	

Table 9 Level of SGPT in sample population

URIC ACID	NO OF CASES	MEAN	STD DEV
3.1 to 5.0	24	54.417	19.662
5.1 to 7.0	26	59.846	21.581
7.0 to 9.0	42	106.214	51.984
>9	8	89.875	60.829
TOTAL	100	P VALUE <0.001	

Table 10 Level of SAP in sample population

URIC ACID	NO OF CASES	MEAN	STD DEV
3.1 to 5.0	24	104.958	36.281
5.1 to 7.0	26	111.231	40.522
7.0 to 9.0	42	158.167	42.038
>9	8	126.625	84.356
TOTAL	100	P value <0.001	

Table 11 Level of Sugar in sample population

URIC ACID	NO OF CASES	MEAN	STD DEV
3.1 to 5.0	24	93.625	11.776
5.1 to 7.0	26	102.038	22.49
7.0 to 9.0	42	99.952	8.859
>9	8	92.75	20.041
TOTAL	100	P value 0.148 not significant	

Table 12 Level of urea in sample population

URIC ACID	NO OF CASES	MEAN	STD DEV
3.1 to 5.0	24	29.458	7.095
5.1 to 7.0	26	27.423	7.829
7.0 to 9.0	42	31.024	5.493
>9	8	32.625	3.926
TOTAL	100	P value 0.094 not significant	

Table 13 Level of Creatine in sample population

URIC ACID	NO OF CASES	MEAN	STD DEV
3.1 to 5.0	24	0.892	0.301
5.1 to 7.0	26	0.912	0.297
7.0 to 9.0	42	0.769	0.199
>9	8	0.937	0.385
TOTAL	100	P value 0.093 not significant	

In this study group hypercholesterolemia associated well with the increased uric acid evels. P value is significant. P value is <0.001(Table 13).

In this study increased levels of triglycerides associated with increased serum levels of uric acid. P value is significant (P <0.001) (Table 14).

In this study population hyperuricemia associated with increased number of cases of cirrhosis. But the p value is 0.696 which is not significant (Table 15).

In this study increased number of patients seen both in lower and higher levels of uric acid. This has no clinical significance.

Table 14 Level of cholestrol in sample population

URIC ACID	NO OF CASES	MEAN	STD DEV
3.1 to 5.0	24	132.458	35.545
5.1 to 7.0	26	161.385	37.709
7.0 to 9.0	42	201.786	22.118
>9	8	221.125	39.228
TOTAL	100	P VALUE <0.001	

Table 15 Level of triglycrides in sample population

URIC ACID	NO OF CASES	MEAN	STD DEV
3.1 to 5.0	24	131.5	27.707
5.1 to 7.0	26	147.692	31.347
7.0 to 9.0	42	205.619	46.098
>9	8	199.125	59.896
TOTAL	100	P VALUE <0.001	

Table 16. Level of cirrhosis against uric acid levels

URIC ACID	CIRRHOSIS
3.1 to 5.0	6
5.1 to 7.0	12
7.0 to 9.0	23
>9	4

P VALUE 0.696 NOT SIGNIFICANT

Table 17 Level of cirrhosis and fatty liver in sample populations

URIC ACID	Male		Female	
	Cirrhosis	Fatty liver	Cirrhosis	Fatty liver
3.1 to 5.0	2	13	4	4
5.1 to 7.0	8	10	1	2
7.0 to 9.0	24	18	11	14

In this study group male patients with increased levels of uric acid associated well with cirrhosis and fatty liver (Table 16). This is significant, this study in female population had strong association with increased uric acid levels and cirrhosis and fatty liver. This is significant value (Table 17).

DISCUSSION

Uric Acid And Gender: Out of the 100 patients studied, the mean uric acid in the total population is 6.73, of which men had higher mean uric acid level when compared to female. But there was no statistical significance between these two groups.

Uric Acid And Age: The mean age in the study group was 46.81years. The mean age formale are 47.52 years and the mean age for the female are 44.68 years. Menhad higher mean age compared to women. The mean age of onset of liver disease is higher in male compared to female. In our study it was observed that uric acid levels increase with age inmale. But exact age group could not be identified (Boyko and Lee, 2006 and Nguyen *et al.,* 2009).

Risk Factors And Uric Acid: In this study hyperbilirubinemia, hypercholesterolemia, BMI, waistcircumference significantly associated with hyperuricemia. Our study did not showed any positive correlation of smoking with hyperuricemia. Dharma *et al* has showed similar results. Body mass index showed statistically significant association with uric acid levels. It was observed that subjects with BMI of 25 associated will with hyperuricemia. 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. Many studies done in this association of BMI with uric acid showed proven results. According to our observation uric acid is useful in identifying cardiovascular risk in people with high BMI (NHANES 1999-2000; Ruhl and Everhart, 2005 and Ruhl and Everhart, 2009). In our study we have not included any risk factors. So hyperuricemia in high BMI is one the risk factors for the development of metabolic syndrome in future. In our study we observed that nonalcoholic patients with ultrasonagram findings of cirrhosis had increased uric acid levels in both the sex. This clearly shows the association of hyperuricemia in cirrhosis. It indicates thatin advanced liver diseases due to the oxidative stress and endothelialdys function serum uric acid level also increases.

In our study we also observed that people with fatty liver also had associated high uric acid levels. 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 study it has been found that uric acid has a significant correlation with BMI, waist circumference and hypercholesterolemia. Hyperuricemia is also associated with both alcoholic and nonalcoholic liver diseases due to increased oxidative stress and inflammatory actions. This study also concluded that hyperuricemia is associated with increased number of cases both with cirrhosis and fatty liver. This clearly indicates that hyperuricemia in fatty liver patients, who are nonalcoholic have considerable risk for future progression to cirrhosis of liver. Because of its association with BMI, waist circumference and hypercholesterolemia, hyperuricemia may be considered as one the risk factor for metabolic syndrome.

Limitations of the Study

In this study progression of the disease in both male and female age group could not be identified properly. We are also not able to correlate the association of other investigations like renal function tests. Ultrasonagram findings not well correlated with age and sex group. Further confirmation of the study needs liver biopsy.

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