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Association between Serum Uric Acid and Non- Alcoholic Fatty Liver Disease and Its Correlation with Liver Fibrosis As Assessed By Fibroscan

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I. Introduction

Non alcoholic fatty liver disease (NAFLD) is one of the common causes for chronic liver disease. The prevalence of NAFLD has increased during last 20 years , ranging from 5% to 25% in Asian countries, depending on the population studied.

NAFLD is diagnosed when daily alcohol consumption is≤30 g/ day in men and ≤20 g/day in women and with exclusion of other causes of disease such asviral hepatitis autoimmune hepatitis, , steatogenic drugs, etc. It is characterized by excessive accumulation of triglyceride (>5%) in the hepatocytes, ranging from hepatic steatosis (Fatty Liver) which may lead on to non alcoholic steatohepatitis (NASH), fibrosis, and liver cirrhosis & hepatocellular carcinoma (HCC).

Multiple "hits", having metabolic syndrome as a major role and inflammation process involving cytokines, adipokines, oxidative stress are hypothesized to explain the complex pathogenesis and progression of NAFLD. NAFLD, widely considered as liver manifestation of metabolic syndrome, is associated with some clinical conditions. Obesity, hypertension, diabetes, dyslipidemia are the most reviewed factors associated with NAFLD.

The final product of purine metabolism in humans, uric acid, is associated with metabolic disorders. It is widely known that increased serum uric acid levels often co-exist with insulin resistance, atherosclerosis, hypertension, and obesity. Inflammation and oxidative stress are hypothesized to be the essential link in this relationship. Recently, several observational studies suggest that hyperuricemia (serum uric acid (SUA) level>7.0 mg/dL in men and >5.7 mg/dL in women) is a risk factor for NAFLD among eastern Asian populations independent of the components of metabolic syndrome

So the main goal of this study is to find the association between serum uric acid and newly diagnosed NAFLD patients attending Outpatient department in Government Rajaji Hospital, Madurai and to find its correlation with liver fibrosis which is assessed by Fibroscan.

Aim Of The Study:

- To determine the association between ultrasound defined NAFLD and serum uric acid
- To find the correlation between serum uric acid level and severity of NAFLD by assessment of liver fibrosis by Fibroscan

II. Materials And Methods

100 ultrasound defined newly diagnosed NAFLD patients attending outpatient department in GRH, Madurai and 100 age and sex-matched healthy subjects with the fulfilment of inclusion criteria and exclusion criteria were included in the study

STUDY DESIGN: Hospital based prospective case control study
STUDY DURATION: 6 Months (March 2018 to August 2018)

INCLUSION CRITERIA:

- All newly diagnosed cases of ultrasound defined NAFLD
- Age group of 25 to 65

EXCLUSION CRITERIA:

- Patients with/on
- Alcohol consumption greater than 20gm/day in men & 10gm/day in women
- HBsAg & Anti HCV positivity
- History of chronic liver disease
- History of Coronary Artery disease, Chronic kidney disease
- On diuretics
- On anti gout medications
- On Anti Retroviral therapy

LABORATORY INVESTIGATIONS

- Random Blood sugar, Fasting & post prandial blood sugar
- Fasting lipid profile
- Serum uric acid
- Serum Bilirubin, SGOT,SGPT, ALP
- Blood urea, serum creatinine
- Complete blood count
- Viral markers (HBsAg, Anti HCV)
- Ultrasonography of abdomen
- Fibroscan

Data Collection

Informed consent will be obtained from all patients to be enrolled for the study. In all the patients relevant information will be collected in a predesigned proforma. The patients are selected based on clinical examinations, biochemical tests and ultrasound abdomen. Then above mentioned lab investigations were done

Statistical Analysis:

Master chart was prepared with all the information collected about the selected cases .With the help of computer Data analysis was done by using SPSS software and Sigma Stat 3.5 version (2012). Using this software, percentage, mean, standard deviation and `p' value were calculated through Student 't' test, One way ANOVA, Pearson Correlation and Chi square test and P value of < 0.05 was taken as significant.

III. Observation And Results

1.AGE DISTRIBUTION:

Age in years	No of Cases	
	Male	Female
26-35	2	3
36-45	24	17
46-55	26	21
56-65	4	3

Most cases of NAFLD (47 patients) occur in 46-55 years of age group (47%)

2. Age distribution for Controls

Age in years	No of Controls	
	Male	Female
26-35	3	3
36-45	24	18
46-55	24	20
56-65	4	8

Again, in control group, most patients are from 46- 55 years of age (44%)

Table 3: Sex Distribution

	No of Cases		No of Controls	
	Male	Female	Male	Female
Number	56	46	55	45

Among 100 cases, 56 were males and 44 were females, while in 100 controls, 55 were males and 45 were females

Table 4:BMI distribution of cases and controls

BMI	No of Cases		No of Controls	
	Male	Female	Male	Female
BMI<25	31	26	39	36
BMI≥25	25	18	16	9

46 patients(46%) were obese in NAFLD cases when compared with 25 patients (25%) in control group

Table.5 Fasting triglyceride level distribution

TGL	No of Cases		No of Controls	
	Male	Female	Male	Female
TGL < 150	18	12	25	23
TGL 150-199	12	12	18	14
TGL ≥ 200	26	20	12	18

46 patients (46%) in case group was found to have hypertriglyceridemia (Triglycerides >200) versus 30 patients (30%) in control group

Table 6. FBS distribution

FBS	Case		Control	
	Male	Female	Male	Female
FBS<100	34	32	43	37
FBS≥100	22	12	12	8

Among NAFLD cases 36 patients (36%) has elevated FBS levels while 20 patients (20%) in control group have elevated FBS levels

Table 7. Systolic blood pressure distribution

SBP	Case		Control	
	Male	Female	Male	Female
SBP<130	44	34	44	38
SBP≥130	12	10	11	7

Elevated Systolic blood pressure is present in 22 cases (22%) and 18 patients (18%) in control group

Table 8 ALT Distribution

ALT	Case		Control	
	Male	Female	Male	Female
ALT< 35	32	33	46	39
ALT≥ 35	24	11	9	6

Among NAFLD cases, 35 patients (35%) have elevated ALT levels while 15 patients have elevated ALT in control group

Table 9. AST distribution

	Case		Control	
	Male	Female	Male	Female
AST < 40	44	37	45	40
AST ≤ 40	12	7	10	5

Among NAFLD cases, 19 patients(19%) have elevated AST levels while 12 patients (12%) have elevated AST levels in control group

Table 10. Distribution of Serum Uric Acid levels

	Case		Control	
	Male	Female	Male	Female
Hyperuricemia	36	28	14	8
Normouricemia	20	16	41	37

In our study, 64 patients (64%) in NAFLD cases have hyperuricemia while in control group, 22 patients (22%) have elevated uric acid levels

Table11: Association of FBS in cases and controls

FBS		
	Case	Control
Mean	93.86	88.03.
SD	13.65	11.59
p value	<0.05	Significant

The mean FBS in case group is 93.86 mg/dL & the mean FBS value in control group is 88.03mg/dL. There is a statistical significance ($p<0.05$) between both the groups

Table 12: Association of BMI in case & controls

BMI	No. of cases	
	Case	Control
Mean	24.463	23.68
SD	1.45	1.44
p' value	< 0.05	Significant

The mean BMI in NAFLD cases is 24.46 kg/m2 while it is 23.63 kg/m2 in control group which again shows statistical significance ($p<0.05$) between two groups

Table 13: Association of systolic BP in case and controls

SBP	No. of cases	
	Case	Control
Mean	121.42	116.52
SD	6.38	9.71
p value	< 0.05	Significant

The mean systolic BP in case group is 121.42mmHg while it is 116.52mmHg in control group. Again, there is a statistical significance between two groups

Table 14:Serum uric acid level in Male case and controls

Male		
Serum uric acid	Case	Control
Mean	6.959	5.875
SD	0.634	1.077
p value	< 0.001 Significant	

In males, the mean serum uric acid level is 6.959 mg/dL in NAFLD cases while it is 5.875 in control group. Again, there is a high statistical significance ($p < 0.001$) between two groups

Table 15: Serum Uric acid level in female case and controls

Female		
Serum uric acid	Case	Control
Mean	5.75	4.931
SD	0.634	0.953
p value	< 0.001 Significant	

In females, the mean serum uric acid level is 5.75 mg/dL while it is 4.93 in control group. There is also statistical significance ($p<0.001$) between two groups

Table 16:Association of Serum Uric acid level in case and control (overall)

Overall (M & F)	No. of cases	
Serum Uric acid	Case	Control
Mean	6.43	5.45
SD	0.964	1.122
p value	< 0.001 Significant	

The mean serum uric acid levels in NAFLD cases is 6.43 mg/dL while it is 5.45mg/dL in control. There is a high statistical significance ($p<0.001$) between two groups

Table :17 Association of fibrosis and serum uric acid

Association of Fibrosis and Serum Uric Acid			
Serum Uric Acid	Fibrosis		Total
	Present	Absent	

Hyperuricemia	28	36	64
Normouricemia	3	33	36
Total	31	69	100
Chi square value	4.127		
p value	0.042	Significant	

The association between hyperuricemia and fibrosis is assessed by chi- square test. The chi square value is 4.127 and the p value is 0.042 ($p<0.05$) which is statistically significant

IV. Discussion

Non Alcoholic Fatty Liver Disease is often considered as the hepatic manifestation of metabolic syndrome with insulin resistance playing a dominant role.As a result of insulin resistance, action of insulin on hormone sensitive lipase is attenuated resulting in increased efflux of free fatty acids into hepatocytes. Within the hepatocytes, free fatty acids attenuate the downstream insulin signalling pathway ultimately resulting in insulin resistance and is then converted to triglycerides in liver. Moreover the action of AMP deaminase is stimulated which results in ATP depletion and increased production of uric acid. Uric acid stimulates the synthesis of IL-1, IL-6, microcyte chemoattractant protein, , TNF alpha , all of which are pro inflammatory molecules. Hence uric acid results in oxidative stress resulting in inflammation andnecrosis. Repeated bouts of inflammation ultimately results in fibrosis

In our study population of 100 NAFLD cases were diagnosed with the help of ultrasound and various parameters were measured. Along with them, 100 age and sex matched controls were taken in to study and various parameters were measured with primary importance to uric acid level. The following observations were made from the study

Age Distribution

Both in cases and controls, most of them were in age group of 46 to 55 years of age. This shows that NAFLD is more prevalent in late middle age group.

Sex distribution

There was a higher incidence of NAFLD in males (56%) when compared with females (44%) in our study

Liver function tests

The mean ALT level in our cases is 34.44 U/L while it is 30.39 U/L in control group. There is a statistically significant difference between both the groups ($p<0.05$)

The mean AST level in NAFLD cases is 35.81 U/L while in the control group, the mean valve is 34.28 U/L and there is a statistical significance between both the values.

Thus, our study shows that AST, ALT levels were abnormal in NALFD cases.

This observation also seen in study done by Shih et al

Fasting triglycerides.

The mean triglycerides level in NAFLD case is 184.19 mg/dL while it is 162.03mg/dL in control group. There is a statistical significance ($p<0.05$) between both the groups. Our study shows that fasting triglycerides were abnormally high in case group which might reflect increased prevalence of metabolic syndrome in NAFLD cases. This observation is also seen in Shih et al

Body Mass index

The mean BMI in NAFLD cases is 24.46 kg/m2 while it is 23.63 kg/m2 in control group which again shows statistical significance ($p<0.05$) between two groups. Hence our show shows increased prevalence of obesity in case group which might be a component of metabolic syndrome. This observation is consistent with the study done by Bansal et al which is held in central India

Fasting blood sugar

The mean FBS in case group is 93.86 mg/dL & the mean FBS value in control group is 88.03mg/dL. There is a statistical significance ($p<0.05$) between both the groups. This observation shows that there may be increased risk of impaired fasting glucose in NAFLD cases. This observation is consistent with the study done by Shih et al.

Systolic Blood pressure

The mean systolic BP in case group is 121.42mmHg while it is 116.52mmHg in control group. Again, there is a statistical significance between two groups. Since hypertensive patients were not taken into study, this might translate into increased prevalence of pre hypertension in NAFLD cases. This observation is also seen in study done by J Liang et al and Shih et al

Serum Uric Acid

The mean serum uric acid levels in NAFLD cases is 6.43 mg/dL while it is 5.45mg/dL in control. There is a high statistical significance ($p<0.001$) between two groups.

In males, the mean serum uric acid level is 6.959 mg/dL in NAFLD cases while it is 5.875 in control group. Again, there is a high statistical significance ($p < 0.001$) between two groups

In females, the mean serum uric acid level is 5.75 mg/dL while it is 4.93 in control group. There is also statistical significance ($p<0.001$) between two groups. Hence our study shows there is higher prevalence of hyperuricemia in NAFLD cases in both males & females. Numerous studies done by Bansal et al, Huang et al, Shih et al, J Liang et al also supports this observation

Serum Uric acid and fibrosis

In 100 NAFLD patients, Fibroscan was done and the Liver stiffness value > 7 kPa was taken as a cut off value for fibrosis. The association between hyperuricemia and fibrosis is assessed by chi- square test. The chi square value is 4.127 and the p value is 0.042 ($p<0.05$) which is statistically significant. Study done by Huang et al demonstrates the association between severity of NAFLD as assessed by liver biopsy and serum uric acid. However no studies have yet demonstrated the association of serum uric acid & fibrosis assessed by fibroscan. Hence further studies are needed to strengthen this association

Thus uric acid level not only help in detection of non alcoholic fatty liver disease , but also helps in predicting the severity of liver fibrosis which can be assessed non invasively by fibroscan.

V. Limitations of the Study

This study has its own limitations. T he sample size is relatively small. More over, the study population involved patients who are seeking medical attention in our hospital which is a tertiary care centre. Hence, they may not represent general population. Also it a single centre study. Hence study in multiple centre with large sample size may be needed to confirm the findings of our present study

Summary:

This prospective case control study was conducted to study "Association between serum uric acid and non-alcoholic fatty liver disease and its correlation with liver fibrosis as assessed by fibroscan"

The study population consisted of 100 NAFLD patients attending General Medicine OPD as cases with age and sex matched individuals as controls. After an institutional ethical clearance and informed consent, various investigations pertaining to the study is done. The data were entered in Microsoft Excel sheet and statistically analysed

The most common age group of NAFLD cases were from 46-55 years of age. There is a slight male predominance in the study. There is a statistically significant difference between cases and controls that involves various parameters of metabolic syndrome such as fasting blood sugar, fasting triglycerides, systolic BP and BMI.

The mean serum uric acid of NAFLD cases is 6.43mg/dl while that of the control is 5.45 mg/dl. There is a statistically significant difference of serum uric acid levels between the NAFLD cases and controls ($p<0.001$). Also there is a significant association between serum uric acid and fibrosis in NAFLD cases as assessed by chi square test ($p<0.05$)

Thus hyperuricemia is significantly associated with non alcoholic fatty liver disease & with fibrosis

VI. Conclusion:

This study shows significant correlation between serum uric acid & NAFLD. Serum uric acid is relatively inexpensive test and is readily available. It is used mainly for detecting gout. However this study shows that presence of hyperuricemia should alert the possibility of underlying non alcoholic fatty liver disease if significant alcohol consumption is ruled out.

Several studies also supports this association. If hyperuricemia proves to be in the causal pathway for NAFLD, then prevention or treatment of hyperuricemia may reduce the risk of development or progression of NAFLD. If hyperuricemia proves to be a consequence of NAFLD, then hyperuricemia could serve as a trigger for physicians to screen for NAFLD.

Also there is linear association between hyperuricemia and presence of liver fibrosis as assessed by fibroscan. Hence uric acid levels play a vital role in detection of NAFLD and its the severity. However further studies are needed to define this association

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