

# Correlation of serum uric acid level with non-alcoholic fatty liver disease (NAFLD) in patients attending at a tertiary level hospital

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## Article Info

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## Abstract

Non-alcoholic fatty liver disease (NAFLD) is considered as a common cause of chronic liver disease. It is potentially progressive towards non-alcoholic steatohepatitis (NASH), hepatic fibrosis, cirrhosis and its complications including hepatocellular carcinoma (HCC). So, the need for predictive factors of NAFLD is important. Among the different serum markers in NAFLD, serum uric acid (SUA) has emerged as a possible predictor of severity of liver damage. This observational cross sectional study was carried out involving 100 patients from the department of gastroenterology, BSMMU, Dhaka, with the intention to determine the association of serum uric acid (SUA) level with non-alcoholic fatty liver disease. Among them, 55 were having NAFLD; and 45 subjects without NAFLD were considered as control. The diagnosis of NAFLD was based on the guidelines for the assessment and management of NAFLD in the Asia-pacific region. Serum uric acid, liver enzymes, glycaemic status, serum lipid profile and anthropometric measurements were compared between NAFLD group & control. The mean age was found  $41.34 \pm 10.88$  years in both the groups. Male were 62% & female were 38% among the study population. Forty percent of the study subjects were overweight, 23% were obese and 37% had normal body weight. NAFLD patients had significantly higher serum uric level ( $6.9 \pm 0.89$  mg/dl) in comparison to non-NAFLD group ( $4.3 \pm 0.87$  mg/dl). The study showed that serum uric acid level was significantly associated with NAFLD. Serum uric acid may be used as a useful additional marker to assess the risk of development of NAFLD in the clinical setting of metabolic syndrome.

## Introduction

Non-alcoholic fatty liver disease (NAFLD) comprises a spectrum of pathological conditions including simple steatosis, nonalcoholic steatohepatitis (NASH) and cirrhosis influencing approximately 20-30% of the general population and its prevalence is increasing worldwide.<sup>1</sup> NAFLD is an emerging problem in the Asia Pacific region and the prevalence is likely to increase in future.<sup>2-3</sup> Simple steatosis is generally a benign condition; however, NASH can progress to cirrhosis and liver failure<sup>4</sup> and the 5-year survival rate for individuals diagnosed with NASH is estimated to be only 67%.<sup>5</sup> NAFLD is often asymptomatic and detected only by abnormal liver function or imaging results in health checkups or during follow-up for other diseases. Patients with elevation of serum aspartate amino-

transferase (AST) and alanine aminotransferase (ALT), high AST/ALT ratio and fatty changes on ultrasonography (USG) or computed tomography (CT) without a history of alcohol intake or positive hepatitis virus markers or autoantibodies can be suspected as having NAFLD.<sup>6,7</sup>

NAFLD is strongly associated with T2DM. The coexistence of NAFLD and T2DM is clinically important for the following reasons: 1) T2DM is an important predictor of development of hepatic fibrosis in patients with NAFLD<sup>(8)</sup> and 2) the presence of T2DM is pivotal with respect to increased risks of cardiovascular disorders and the development of hepatocellular carcinoma in the setting of NAFLD.<sup>9,10</sup> There is evidence that suggests elevated serum uric acid (SUA) is commonly associated with the development or progression of NAFLD.<sup>11,12</sup>

NAFLD is now considered a part of metabolic syndrome, a clustering of cardiovascular disease risk factors closely associated with insulin resistance and many endocrine derangements including glucose homeostasis and central obesity.<sup>13-16</sup>

Uric acid is the end product of purine metabolism and is formed from xanthine oxidoreductase. However emerging evidence suggests that increased uric acid, despite being a major antioxidant in the human plasma<sup>17</sup> is associated with cardiovascular disease<sup>18</sup>, diabetes<sup>19</sup> and metabolic syndrome<sup>20</sup> as well as conditions linked to oxidative stress, chronic low grade inflammation and insulin resistance. Macrovascular fat accumulation in more than 5% of hepatocytes is the defining feature of NAFLD.<sup>21</sup> Significant alcohol intake should be excluded before the diagnosis of NAFLD. Along with the "obesity epidemic", the worldwide prevalence of NAFLD, based on imaging studies, is increasing rapidly and now includes 14-31% of the general population.<sup>22</sup> It is generally imputed to obesity-induced insulin resistance. Some observational studies showed that hyperuricemia is a risk factor for NAFLD among eastern populations irrespective of the components of metabolic syndrome.<sup>23</sup> In fact, there is some evidence that insulin resistance can lead to reduced excretion of serum uric acid and increased serum uric acid level.

NAFLD is the most common liver disease identified in western countries. Present understanding of natural history of NAFLD is based on studies in whites who became overweight or obese and developed metabolic syndrome in adulthood. Some studies also suggest that the risk for NAFLD and NASH related cirrhosis may be higher in certain ethnic groups such as Asians, certain Hispanics, and native Americans.<sup>24</sup> Mounting evidence suggests that elevated serum uric acid (SUA) is frequently associated with the development or progression of metabolic syndrome (MS).<sup>25-26</sup> Serum uric acid is the body's main antioxidant. Oxidative stress and lipid peroxidation injury is one of the important pathogenesis pathways of NAFLD.<sup>22</sup> However the relationship between serum uric acid and NAFLD is still controversial, therefore, the research on the relationship between serum uric acid and NAFLD has important significance for the prevention and diagnosis of NAFLD. Very few studies have been conducted in our community to know the association of serum uric acid (SUA) with nonalcoholic fatty liver disease (NAFLD). The result of this study will be applicable to our patients of NAFLD and the impact of the result will help to identify the disease earlier and to take necessary measures to prevent NAFLD.

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## Methodology

This observational cross-sectional study was carried out in the department of Gastroenterology, BSMMU, Dhaka during the period of October 2016 to March 2017. Patients who underwent abdominal ultrasonography due to various

reasons & diagnosed to have fatty liver in ultrasonography were initially included in the study.

In this study, fatty liver disease was recognized by the presence of at least 2 of 3 abnormal findings on abdominal ultrasonography i.e. 1. diffusely increased liver echogenicity with greater liver echogenicity than kidney or spleen echogenicity 2. Vascular blurring & 3. Deep attenuation of the ultrasound signal.<sup>27</sup> Ultrasonographic outcome was determined by at least two experienced radiologists who were blinded to the laboratory values of the examinees.

The diagnosis of NAFLD was based on the guidelines for the assessment and management of NAFLD in the Asia-pacific region i.e. (1) Imaging findings of fatty liver disease (2) Absence of excessive alcohol consumption (ethanol intake <140g/week for men and 70 g/week for women) and (3) exclusion of diseases leading to steatosis, such as hepatitis B, hepatitis C, alcohol-related liver disease, autoimmune hepatitis and haemochromatosis.<sup>27</sup>

A total of 55 patients with NAFLD meeting the above mentioned criteria were included in the study. Another 45 patients who were not found to have fatty liver in abdominal ultrasonography, and who also met all the inclusion & exclusion criteria, were included in the study as control.

The laboratory measurements included serum uric acid, fasting plasma glucose (FPG), OGTT, HbA1c, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), total cholesterol (TC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT). Anthropometric measurements including body mass index (BMI) were calculated in both NAFLD group & control.

Those with serological markers of hepatitis B or C virus, alcohol consumption greater than 140 g/week, known liver disease because of another etiology, history of cancer or taking chemotherapy, pregnant women, patients taking diuretics, low dose aspirin, cyclosporine, pyrazinamide, ethambutol, allopurinol, history of treatment with exogenous estrogen or tamoxifen, febuxostat, known case of renal failure or gout were excluded from this study.

Serum uric acid, liver enzymes, glycaemic status, serum lipid profile and anthropometric measurements were compared between NAFLD group & control.

Written informed consent was obtained from all participants. The study protocol was approved by the Institutional Review Board of BSMMU.

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## Results

This cross sectional observational study was carried out in the department of Gastroenterology, BSMMU, Dhaka, Bangladesh

involving 100 patients attending the inpatient and outpatient departments. Majority of patients incorporated in this study belongs to age group between 36-45 years (33%) followed by 26-35 years group (which was 26%). Mean age was  $41.34 \pm 10.88$  years (Table-I). Males (62%) were predominant than females (38%) (Table 3). 40% of study subjects were overweight, 23 % were obese and 37 % were normal weight (Figure-1 & Table-II).

55% of study population had fatty liver on ultrasonography and categorized as nonalcoholic fatty liver disease (NAFLD). Liver ultrasonography was normal in 45 out of 100 patients. In male patients (n=62), hyperuricaemia was found in 22 (35.49%) and normal serum uric acid concentration was observed in 40% patients (64.51%) (Table-IV). Among female, (n=38) 29 patients had normal serum uric acid (76.31%) and 9 patients were hyperuricaemic (23.69%) (Table-IV). In NAFLD group (n=55) 23 patients were hyperuricaemic (41.82%) and 32 patients had normal serum uric acid level (58.18%).

In normal group (n=45) 8 patients had hyperuricemia (17.78%) and 37 patients had normal (82.22%) serum uric acid level (Table 4). In NAFLD group, mean serum uric acid concentration was  $6.9 \pm 0.89$  mg/dl and in normal group it was  $4.3 \pm 0.87$  (Table -IV). Difference between serum uric acid level in NAFLD group and normal group was statistically significant ( $p < 0.001$ ).

Out of 100 patients, 23 were diabetic, 41 had IGT and 36 had normal glycaemic status (Table-IV). In NAFLD group, diabetes, IGT and normal glycaemic status was 39.91%, 49.09% and 20% respectively. In normal group, diabetes, IGT and normal glycaemic status was 13.34%, 31.11% and 55.55% respectively (Table-IV). Mean fasting blood sugar (FBS) of the respondents was  $6.03 \pm 0.66$  mmol/l with range of 4.8-7.3 mmol/l (Table-IV). Mean postprandial blood sugar of study population was  $8.9 \pm 0.76$  mmol/l with the range of 7.6-11.6 mmol/l. Mean HbA1c was  $6.1 \pm 0.2$  mmol/l.

Mean fasting blood sugar of NAFLD group was  $6.81 \pm 2.07$  mmol/l and in normal group was  $5.26 \pm 1.88$  mmol/l. The difference of these two group was statistically significant ( $p$  value  $< 0.001$ ). Mean 2hrs postprandial blood glucose of NAFLD group was  $10.15 \pm 3.69$  mmol/l and in normal group was  $7.65 \pm 3.69$  mmol/l. The difference between these two groups was statistically significant ( $P$  value  $< 0.001$ ) (Table-IV).

In NAFLD patients the mean ALT, AST, GGT and ALP were  $55 \pm 12.45$  u/l,  $45 \pm 11.29$  u/l,  $165 \pm 12.24$  u/l, and  $96 \pm 23.71$  u/l respectively. On the other hand, the mean ALT, AST, GGT and ALP level were  $25 \pm 19.11$  u/l,  $25 \pm 17$  u/l,  $28 \pm 22.43$  u/l and  $85 \pm 22.50$  u/l respectively (Table-5). In this study, the mean levels of hepatic enzymes were higher in the NAFLD group

except ALP level. Significant relationship was observed with NAFLD (Table-IV).

Table III shows 55 (55%) patients had fatty liver on liver ultra ultrasonography and categorized as NAFLD of whom 35 were

Table-I		
Distribution of patients by age (n=100)		
Age of the patient (yrs)	Total no. of patient	Percentage
16-25	09	09
26-35	26	26
36-45	33	33
46-55	18	18
56-65	13	13
66-75	01	01
Total	100	100
Mean $\pm$ SD	$41.34 \pm 10.88$	

Table I Shows Majority of the patients incorporated in this study belongs to age group between 36 - 45 years (33%), followed by 26 - 35 years group (26%).

Table-II			
Comparison of demographic parameters and BMI between NAFLD and non-NAFLD group (n=100)			
	NAFLD (n=55)	Non-NAFLD (n=45)	P
Age (mean $\pm$ SD)	$40.38 \pm 8.28$	$42.29 \pm 9.37$	0.536
M:F	1.2:1	1.25:1	0.452
Waist (cm)	$84.17 \pm 8.15$	$73.15 \pm 7.17$	$< 0.001$
BMI	$25.10 \pm 1.75$	$21.64 \pm 2.62$	$< 0.001$

Table-III			
Distribution of patients as per liver ultrasonography across sex category (n=100)			
Sex	Liver ultrasonography <sup>a</sup>		Total
	NAFLD (%) <sup>b</sup>	Non-NAFLD (%) <sup>b</sup>	
Male	35 (63.63%)	27 (60%)	62
Female	20 (36.37%)	18 (40%)	38
Total	55 (100%)	45 (100%)	100

a: According to liver ultrasonography findings patients were categorized as Non Alcoholic Fatty Liver Disease-NAFLD (fatty liver) and normal liver

b: Represents percentage of subject. in respective category.

male and 20 were female. 45 patients had normal findings on liver ultrasonography categorized as normal of whom 27 were male and 18 were female.

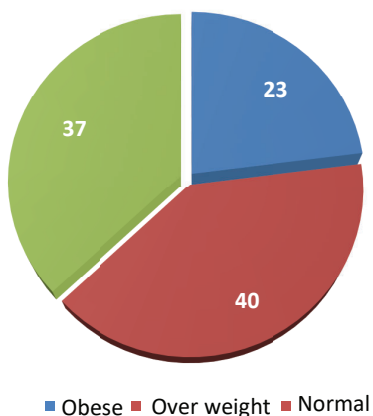


Fig-1: Distribution subjects according to BMI

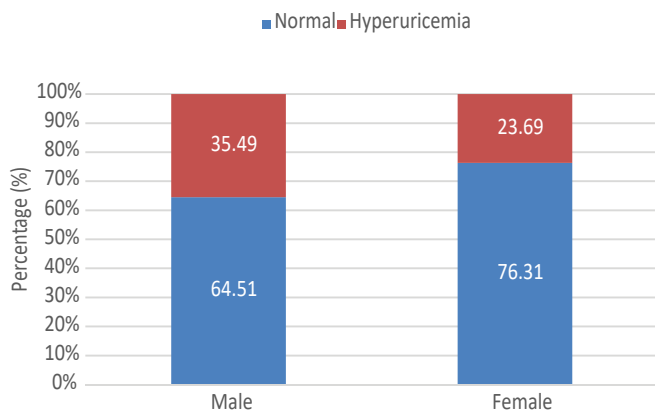


Fig-2: Hyperuricemia in male and females (n=100)

Table-IV		
Distribution of subjects according to glycaemic status and serum uric acid level between NAFLD (n=55) and non-NAFLD (n=45)		
	NAFLD	Non-NAFLD
Glycaemic status		
Normal	11(20%)	25 (55.55%)
IGT	27(49.09%)	14 (31.11%)
Diabetes	17(39.91%)	06 (13.34%)
Serum uric acid level		
Normal	32 (58.18%)	37 (82.22%)
Hyperuricaemia	23 (41.82%)	08 (17.78%)

Table-V			
Comparison of biochemical parameters between NAFLD and non- NAFLD group (n=100)			
	NAFLD	Non-NAFLD	P
FBS (mmol/L)	6.81±2.07	5.26 ± 1.88	<0.001
2 hours post prandial blood sugar (mmol/L)	10.15 ± 3.69	7.65 ± 3.69	<0.001
HbA1c (%)	6.89 ± 2.01	5.3 ± 1.68	<0.001
Serum uric acid, mg/dl (mean ± SD)	6.9±0.89	4.3±0.87	<0.001
ALT (U/L)	55±12.45	25±19.11	<0.001
AST (U/L)	45±11.29	30±16.25	<0.001
ALP (U/L)	86±13.71	82±8.50	0.434
GGT (U/L)	65±12.24	28±22.43	<0.001

### Discussion

This hospital based observational study was done to find out correlation of serum uric acid with NAFLD. A total number of 100 patients who fulfilled the inclusion and exclusion criteria attending the department of Gastroenterology during the period of October' 2016 to March' 2017, BSMMU, Dhaka, Bangladesh, were enrolled in this study. Findings of the present study were discussed and compared with previously published relevant studies. Most of the study subjects hailed from different districts of Bangladesh.

In this current study, it was observed that the mean age was found 41.34±10.88 years with range from 20-70 years (Table-1). The majority of population was found between 36-45 years (33%). Out of this 100 subjects 62% were male and 38% were female (Table III).

In this study, out of 100 study patients 55% were found to have fatty liver on ultrasound scan of liver and they were grouped as NAFLD. 45% of respondents were normal on ultrasound scan of liver and fall in another group, termed as normal group. Among NAFLD people 35 patients (63.63%) were male and 20 patients (36.37%) were female. Among, Normal subjects 27 patients (60%) were male and 18 patients (40%) were female (Table III).

A large study (N-1320) that was conducted by Kurata et al<sup>28</sup> in 2005 showed that the majority of population was between 35-48 years and there was 60% male and 40% female. In one study Baba et al.<sup>29</sup> 2007 showed mean BMI of NAFLD patients was 28.30±2.96 kg/m<sup>2</sup>.

In another study Colloredo et al.<sup>30</sup> 2003 showed 53% of study population had NAFLD and 47% of study population were normal groups. 60% were male and 40% were female.

Out of 100 patients, 23 were diabetic, 41 had IGT and 36 had normal glycaemic status. In NAFLD group, diabetes, IGT and

normal glycemic status was 39.91%, 49.09% and 20% respectively. In normal group, diabetes, IGT and normal glycemic status was 13.34%, 31.11% and 55.55% respectively (Table IV). Mean fasting blood sugar (FBS) of the respondents was  $6.03 \pm 0.66$  mmol/l with range of 4.8-7.3 mmol/l. Mean postprandial blood sugar of study population was  $8.9 \pm 0.76$  mmol/l with the range of 7.6-11.6 mmol/l. Mean HbA1c was  $6.1 \pm 0.2$  mmol/l. Mean fasting blood sugar of NAFLD group was  $6.81 \pm 2.07$  mmol/l and in normal group was  $5.26 \pm 1.88$  mmol/l. The difference of these two groups was statistically significant ( $p$  value  $< 0.001$ ). Mean 2hrs postprandial blood glucose of NAFLD group was  $10.15 \pm 3.69$  mmol/l and in normal group was  $7.65 \pm 3.69$  mmol/l. The difference between these two groups were statistically significant ( $P$  value  $< 0.001$ ) (Table V).

The glycaemic status of NAFLD group in our study is supported by one large study conducted by Petta et al<sup>31</sup> in 2011. Another study was done by Matsumoto N et al<sup>32</sup> in 2015 and found abnormal glycaemic status in NAFLD. This also correlates with the current study.

In this study, the mean levels of hepatic enzymes were higher in the NAFLD group except ALP level. Significant relationship was observed with NAFLD. Novakovic et al.<sup>33</sup> in their study showed a significant relationship between hepatic enzymes (ALT, GGT, AST/ALT ratio) apart from AST. Most previous studies have shown that there is a significant relationship between NAFLD and AST[10,16] ALT[10,16,21] and ALP. Zakeri and KarmaratPanah<sup>34</sup> stated that ALT and dyslipidemia might be involved in the prevalence and development of NAFLD. In this study, a significant relationship was observed between hepatic enzymes GGT ( $P = 0.004$ ), ALT ( $P < 0.001$ ), AST ( $P < 0.001$ ).

In our study, 69 patients had normal serum uric acid level and 31 patients had high uric acid level (Table 4). In male subjects 64.51% had normal serum uric acid level and 35.49% had high serum uric acid level. In females, 76.31% had normal serum uric acid level and 23.69% had high serum uric acid level (Figure 2). These observations were in agreement with earlier reports conducted by Li Y et al<sup>35</sup> in 2009.

In NAFLD group 58.18% had normal serum uric acid level and 41.82% had high serum uric acid level. In normal group 82.22% had normal serum uric acid level and 17.78% had high serum uric acid level (Table-IV).

Our study shows higher level of serum uric acid level in NAFLD group than normal group. In NAFLD group mean serum uric acid level was  $6.9 \pm 0.89$  mg/dl and in normal group mean serum uric acid level was  $4.3 \pm 0.87$  mg/dl (Table-V). The difference between these two groups was statistically significant ( $P$  value  $< 0.001$ ).

These findings were consistent with a previous study done by Hwang IC et al<sup>36</sup> in 2011. Lee et al.<sup>37</sup> conducted a study in 2010

and their findings were similar with our study result and found high serum uric acid level in NAFLD.

Another study was done by Li et al.<sup>38</sup> in 2009 and showed serum uric level was significantly associated with NAFLD and elevated serum uric acid is an independent risk factor for NAFLD.

The results of previous studies were consistent with those of our study. Li et al. reported that higher serum uric acid level was associated with NAFLD in 8925 employees of chemical company.<sup>38</sup>

It was speculated that SUA level might be the physiological compensatory mechanism for enhancing patients with NAFLD against oxidative stress. In recent years, some studies found that SUA had strong antioxidant function in the body of patients with metabolic syndrome.<sup>39</sup>

There were several studies which had investigated the role of serum uric acid and hyperuricaemia in the pathogenesis of NAFLD<sup>40</sup>. It had been reported that increased serum uric acid concentrations, even within normal range are independently associated with the presence of NAFLD. In the largest cross sectional study, including 10732 subjects evaluating the relationship between high serum uric acid levels and ultrasound diagnosed NAFLD, there was a strong association between increased serum uric acid level and presence of NAFLD in men and women.

In addition, this association was shown to persist after adjustment of demographic and several potential confounder. Furthermore, hyperuricemia has been shown to be a predictor in a prospective study with 3 and 5 years follow up.<sup>40</sup> However few data were available about the relationship of serum uric acid with histologically diagnosed NAFLD. Further studies need to explain the physiological mechanism for this association.

### Limitations

Although the results of this study support the hypothesis, there are some facts which might affect the result.

1. Small size of the study population and it was single centre study.
2. Study was conducted in a tertiary level hospital which did not represent all groups of the general population. Thus, we did not consider other potential confounding factors on serum uric acid level such as demographic factors and dietary pattern.
3. The diagnosis of NAFLD by ultrasound was relatively insensitive as compared to that by biopsy.

### Conclusion

Our study showed a clear association between NAFLD and serum uric acid level. Serum uric acid level in patients with NAFLD was higher than normal subjects. This study indicated

that increased serum uric acid concentration may be a useful additional marker in assessing the risk of NAFLD in the clinical setting of metabolic syndrome. Further research is warranted for better understanding of its pathophysiologic role in the development of NAFLD. Abnormal glycaemic status and higher level of liver enzymes were also found in NAFLD.

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