

Association of the serum uric acid level with liver histology in biopsy-proven non-alcoholic fatty liver disease

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Abstract. Hyperuricemia is significantly associated with and independently predicts the risk for non-alcoholic fatty liver disease (NAFLD). The aim of the present study was to examine the association of serum uric acid (SUA) levels with liver histology in patients with biopsy-proven NAFLD. Data were collected from 158 adults aged >18 years, and diagnosed with biopsy-proven NAFLD. The differences in liver histology were assessed between hyperuricemic and normal SUA groups with NAFLD to determine the possible risk factors. The SUA level was closely associated with the degree of steatosis (correlation coefficient 0.177, $P=0.027$). A higher proportion of patients with hyperuricemia showed increased severity of lobular inflammation (lobular inflammation score ≥ 2) compared with patients exhibiting normal SUA (75 vs. 52.7%; $\chi^2=8.548$, $P=0.003$). Hyperuricemic groups had higher non-alcoholic steatosis (≥ 5) compared to the normal SUA groups with NAFLD (48.8 vs. 31.1%; $\chi^2=5.131$, $P=0.024$). Hyperuricemia was independently associated with advanced lobular inflammation (odds ratio, 2.79; 95% confidence interval, 1.250-6.257; $P=0.012$) using a logistic regression model controlling for ferritin, serum alanine aminotransferase and aspartate aminotransferase. In conclusion, hyperuricemia is associated with histologically severe NAFLD. Hyperuricemia was independently associated with greater odds of advanced lobular inflammation of NAFLD.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a state of intra-hepatic fat accumulation, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis. NAFLD is the most common liver disease in Western countries, affecting 20-30% of the general population (1). NAFLD is also an emerging public health concern in developing countries (2,3). Among more affluent regions of China, the community prevalence of NAFLD is 15% (2). With the increasing obesity pandemic, the prevalence of NAFLD is likely to increase in the future (2). Serum uric acid (SUA) levels are closely associated with insulin resistance, diabetes mellitus type 2 and metabolic syndrome (4,5). Hyperuricemia was significantly associated with NAFLD, and the prevalence of NAFLD increases with SUA increase (6-8). Elevation in SUA levels independently predicts an increase in the risk for the incident of NAFLD and suggests that high SUA levels may have a causal role in the development of NAFLD (9). Certain *in vitro* and *in vivo* studies in hepatocytes and liver tissue of mice suggest that uric acid stimulated fat synthesis and induced inflammatory cell infiltration in the liver (10,11). Therefore, it is plausible that uric acid may reflect increased disease severity in NAFLD. However, there is one previous study regarding the association between UA serum levels and histological severity of NAFLD patients (12). The majority of studies have been conducted in Western populations. Notably, the prevalence of obesity in China is significantly lower compared to Western countries (13,14), and certain features of metabolic syndrome, such as waist circumference and body mass index (BMI), are defined differently (2,15). Therefore, due to this the previous results should not be compared to the Chinese population. The present study aimed to investigate the association of SUA levels with liver histology in Chinese patients with biopsy-proven NAFLD.

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Abbreviations: NAFLD, non-alcoholic fatty liver disease; SUA, serum uric acid; NASH, non-alcoholic steatohepatitis; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ -glutamyl transpeptidase

Key words: histology, inflammation, non-alcoholic fatty liver disease, uric acid

Materials and methods

Study design and subjects

Patient population. A total of 158 patients (age ≥ 18 years) with well-characterized and liver biopsy-confirmed NAFLD were included in the study. Patients were untreated and consecutively biopsied at the Hangzhou Xixi Hospital Affiliated to

Zhejiang Chinese Medical University (Hangzhou, Zhejiang, China) between 2008 and 2013. The diagnosis of NAFLD was based on the following criteria: Liver biopsy showing steatosis in $\geq 5\%$ of hepatocytes. The exclusion criteria were as follows: Viral hepatitis or autoimmune, alcohol-induced (male >20 g/day; female >10 g/day) or drug-induced liver disease, and cholestatic or metabolic/genetic liver disease. Other liver diseases were excluded using specific clinical, biochemical, radiographic and/or histological criteria.

Clinical and laboratory assessments. Clinical and laboratory parameters were collected on the day of the liver biopsy. A complete medical history and physical examination was undertaken in all patients. Hyperuricemia was defined as an SUA level >360 mmol/l in women and >420 mmol/l in men (16). BMI was calculated as weight (in kilograms)/height (in meters²). A fasting blood sample was obtained from each subject in the morning. Laboratory measurements included serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, γ -glutamyl transpeptidase (GGT) and albumin levels; fasting glucose, complete blood count; total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and total triglycerides; fasting insulin; ferritin levels; viral serology for hepatitis B and C infection; autoantibodies; $\alpha 1$ antitrypsin levels and phenotype. All the values were measured using an Olympus AU640 autoanalyzer (Olympus, Kobe, Japan) adopting the standard methods.

For histological analysis, liver specimens were fixed with 4% buffered paraformaldehyde and embedded in paraffin. Sections of 2 μ m were prepared and evaluated for liver fibrosis by hematoxylin and eosin staining. The histological grading and staging of NAFLD (degree of steatosis, lobular inflammation and hepatocyte ballooning) were scored according to the modified criteria established by Kleiner *et al* (17). The degree of steatosis was assessed using the following scale: 0 (absent, when the extent of steatosis was $<5\%$), 1 (5-33%), 2 (33-66%), and 3 ($>66\%$). The NAFLD activity score (NAS) ranges between 0 and 8, and is represented by the sum of scores for steatosis (0-3), lobular inflammation (0-3) and ballooning (0-2). $NAS \geq 5$ were diagnosed as NASH. Degree of fibrosis was evaluated separately according to the Kleiner and Brunt score (17). Fibrosis was staged as: 0 (none), 1 (portal or zone 3 perisinusoidal fibrosis), 2 (periportal and zone 3 perisinusoidal fibrosis without bridging), 3 (bridging fibrosis) and 4 (cirrhosis). Liver biopsy specimens were analyzed by an expert liver pathologist who was blinded to the biological data and order of biopsy.

Statistical analyses. Continuous variables are presented as mean \pm standard deviation. The association between SUA and variables of interest was examined with uric acid as a dichotomous variable. Continuous variables were compared with Student's t-test or Wilcoxon rank-sum test, depending on the normality of the data. The association between SUA level and histology was determined using Spearman's rank correlation. Categorical variables, including histological features such as steatosis, lobular inflammation grade and fibrosis stage, were analyzed using either Fisher's exact or χ^2 tests. Binary logistic regression analysis (enter; entry: 0.05, removal: 0.10) was used to evaluate the risk factors for NAFLD. All the statistical

analyses were performed using the SPSS software package version 20 for Windows (IBM, Corp., Armonk, NY, USA). $P < 0.05$ (two-tailed) was considered to indicate a statistically significant difference.

Results

Patient profile. A total of 158 adult subjects (aged ≥ 18 years) with biopsy-proven NAFLD (defined as $>5\%$ steatosis) and SUA levels measured within 2 weeks of liver biopsy, were evaluated. The baseline profile, including age, gender, BMI, blood pressure, serum liver enzymes, lipids, glucose and SUA levels, are shown in Table I. Hyperuricemia was identified in 84 subjects (73 males and 11 females). The proportion of normal SUA and hyperuricemia was 46.8 vs. 53.2%, respectively. No other significant differences were observed in SBP/DBP or BMI and the presence of diabetes between normal SUA and hyperuricemia groups.

Association between the serum parameters and SUA levels. Differences in the serum parameters between patients with normal SUA versus hyperuricemia are shown in Table I. Patients with hyperuricemia showed higher hemoglobin and LDL-C, but lower fasting glucose compared to those with normal uric acid levels ($P=0.016$, $P=0.028$ and $P=0.038$, respectively). By contrast, no difference was observed between the groups for GGT, direct bilirubin, fasting insulin, homeostasis model assessment of insulin resistance, white blood cell count and platelet count. Although AST, ALT and serum ferritin in the hyperuricemia group were higher compared to the normal uric acid group, no significance was detected ($P=0.209$, $P=0.089$ and $P=0.335$, respectively).

Association between SUA and histological severity of NAFLD. First, the association of the SUA level and liver histology of all the NAFLD patients was examined. The results showed that the SUA level was closely associated with the degree of steatosis ($P=0.027$) in all patients. The SUA level was possibly associated with NAS and lobular inflammation ($P=0.056$, $P=0.059$), but not with the degree of hepatocyte ballooning and fibrosis ($P=0.689$, $P=0.584$).

Increased histological severity of NAFLD was associated with hyperuricemia. A higher proportion of patients with hyperuricemia showed increased severity of lobular inflammation compared with patients exhibiting normal uric acid levels ($\chi^2=8.548$, $P=0.003$) (Fig. 1). Subjects with hyperuricemia had a higher NAS ($NAS \geq 5$) compared to the normal SUA groups with NAFLD ($\chi^2=5.131$, $P=0.024$) (Fig. 2). Subjects with hyperuricemia were also likely to have a definitive diagnosis of NASH compared to those with normal SUA. However, no significant differences occurred between hyperuricemia and normal SUA groups in terms of the proportion of patients with fibrosis, ballooning and steatosis ($P=0.249$, $P=0.653$ and $P=0.247$, respectively).

To investigate the different levels of SUA independently associated with lobular inflammation and NASH, we used a binary logistic regression analysis, including the following variables, selected a priori, AST, ALT, ferritin and HDL-C, and SUA values represented dichotomous independent variables (normal SUA and hyperuricemia). These results showed

Table I. Characteristics of patients according to different serum uric acid levels.

Variable	Normal SUA	Hyperuricemia	t value	P-value
Age, year	38.52±10.62	34.72±9.81	2.338	0.021
Total, n (male/female)	74 (54/20)	84 (73/11)	4.842	0.028 ^a
BMI, kg/m ²	25.79±2.53	25.68±4.60	0.180	0.858
SBP, mmHg	121.86±11.44	123.48±14.01	-0.698	0.486
DBP, mmHg	79.06±7.42	77.95±10.55	0.672	0.503
Diabetes diagnosis, n	3	2	0.021	0.885 ^a
AST, IU/l	58.50±49.58	68.26±47.62	-1.261	0.209
ALT, IU/l	92.32±94.42	116.77±84.94	-1.713	0.089
WBC, x10 ⁹ /l	6.39±1.74	6.69±1.65	-1.071	0.286
PLT, x10 ⁹ /l	196.39±55.42	203.40±56.57	-0.785	0.434
HB, g/l	14.55±2.00	15.24±1.16	-2.439	0.016
GGT, IU/l	88.47±93.78	84.94±69.02	0.271	0.786
Glucose, mmol/l	5.52±1.46	5.13±0.75	2.090	0.038
Insulin, mIU/l	11.73±7.00	14.06±7.40	-1.788	0.076
TG, mmol/l	2.16±1.31	2.18±1.79	-0.093	0.926
TC, mmol/l	4.92±1.23	5.13±0.99	-1.159	0.248
HDL-C, mmol/l	1.15±0.26	1.20±0.34	-0.962	0.338
LDL-C, mmol/l	2.58±0.92	2.96±0.88	-2.227	0.028
Ferritin, ng/ml	359.21±267.99	404.27±248.11	-0.967	0.335
Uric acid, μmol/l	346.10±53.45	471.13±50.25	-15.101	<0.0001

^aP-values from χ^2 or continuity correction for categorical variables. Data are expressed as mean ± standard deviation, as appropriate. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell count; PLT, platelet count; HB, hemoglobin; GGT, γ -glutamyl transpeptidase; TG, total triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

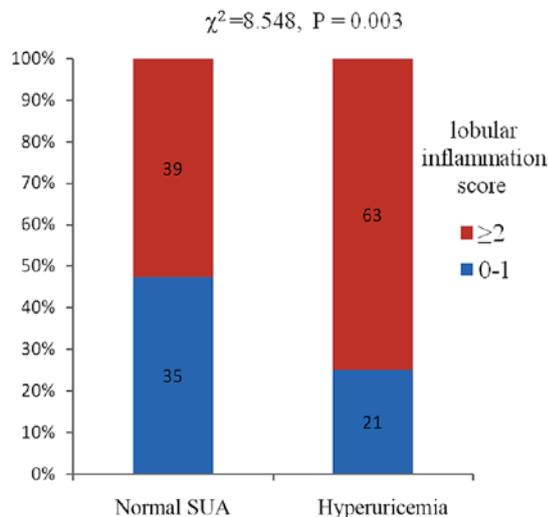


Figure 1. Association between different SUA and the severity of lobular inflammation with non-alcoholic fatty liver disease. SUA, serum uric acid.

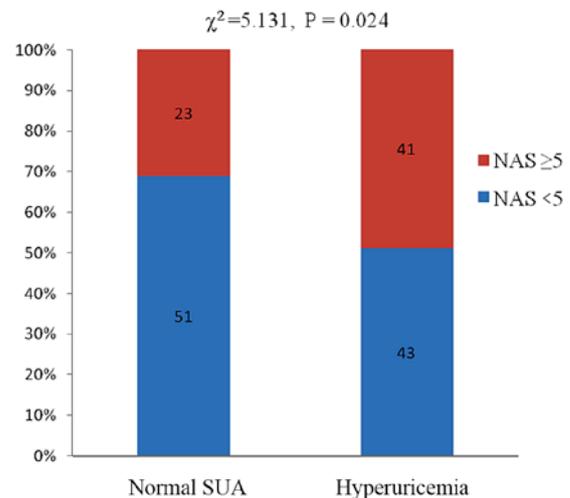


Figure 2. Association between different SUA and NAS with NAFLD. NAFLD, non-alcoholic fatty liver disease; SUA, serum uric acid; NAS, NAFLD activity score.

that hyperuricemia was an independent predictor of advanced lobular inflammation [odds ratio (OR), 2.797; 95% confidence interval (CI), 1.250-6.257; P=0.012] using a logistic regression model controlled for ferritin, serum ALT and AST (Table II). Hyperuricemia was a more likely predictor of NASH diagnosis (OR, 2.28; P=0.052).

Discussion

In the present study, the SUA level was significantly associated with the degree of steatosis in patients with NAFLD. Furthermore, increased SUA levels were associated with a greater severity of lobular inflammation and NASH.

Table II. Independent association of advanced lobular inflammation on logistic regression modeling using different serum uric acid levels.

Variable	B	SE	Wald	P-value	Exp(B)	95% CI for Exp(B)
Uric acid	1.028	0.411	6.265	0.012	2.797	1.250-6.257
AST	0.009	0.009	0.937	0.333	1.009	0.991-1.026
ALT	0.000	0.005	0.002	0.961	1.000	0.991-1.009
Ferritin	0.001	0.001	1.890	0.169	1.001	0.999-1.003

SE, standard error; CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Hyperuricemia was independently associated with an increased risk of severity of lobular inflammation and was a likely predictor of NASH in NAFLD patients.

SUA levels were significantly associated with the degree of steatosis in patients with NAFLD. Uric acid has been shown to contribute to lipoprotein oxidation and inflammation (11,18). Lanaspá *et al* (10) provided the first direct evidence that uric acid stimulated fat synthesis in the hepatocytes and in the pound mouse. The study reported that lowering the hepatic uric acid level reduced fatty liver in the fructose-exposed hepatocytes (10). Another study also indicated that hypouricemic therapy using allopurinol and benzbromarone significantly ameliorated hepatic steatosis and decreased serum cholesterol levels in a Mongolian gerbil model of NAFLD (19). In fact, a population-based prospective study showed that SUA was significantly associated with the development of NAFLD, suggesting that high SUA levels may have a causal role in the development of NAFLD (9). Similarly, the present study demonstrated that the SUA level was significantly associated with the degree of steatosis from a histological perspective.

As aforementioned, the present study identified that increased SUA levels were associated with a greater severity of lobular inflammation in biopsy-proven NAFLD. Another study reported similar findings in Italy (12). The present study observed that hyperuricemia was also possibly linked to higher NAS, implying that hyperuricemia was likely to be associated with a definitive diagnosis of NASH. This result further demonstrated that hyperuricemia was an independent predictor of advanced lobular inflammation (OR, 2.797; 95% CI, 1.250-6.257; P=0.012) using a logistic regression modeling.

Three potential factors explain the association between high SUA levels and severity of lobular inflammation. First, uric acid acts as a strong oxidant. Uric acid activated NADPH oxidase followed by redox-dependent proinflammatory signaling via protein kinase p38 in adipocyte differentiation (18). Soluble uric acid directly stimulated the redox-dependent proinflammatory signaling in adipocytes. Second, SUA induced inflammatory cell infiltration in the liver. Uric acid increased the expression of MCP-1 (an inflammatory agent), and decreased the expression of adiponectin (an anti-inflammatory agent). Third, lowering uric acid in these mice by inhibiting xanthine oxidoreductase improved the balance in the adipose tissue by attenuating MCP-1 levels and increasing the production of adiponectin. In addition, lowering uric acid in obese mice decreased macrophage infiltration in the adipose

tissue and reduced insulin resistance. Hyperuricemia may be partially responsible for the inflammation in the adipose tissue (11). A recent study demonstrated that uric acid crystals induced pro-inflammatory effects (20).

NLRP3 inflammasomes have a pivotal role in triggering innate immune responses in NAFLD. Uric acid crystals activate the NALP3 inflammasome (21). Uric acid is a classic example of the danger-associated molecular pattern. Vandannagsar *et al* (22) found that the NALP3 inflammasome mediated the recognition of certain non-microbial 'danger-signals' leading to caspase-1 activation and interleukin-1 β (IL-1 β) and IL-18 secretion, and contributed to obesity-induced inflammation and insulin resistance. Elimination of NALP3 in obesity reduced IL-18 and adipose tissue interferon- γ along with an increase in naïve T cells and reduction in effector adipose tissue T cells. Uric acid stimulated NLRP3 inflammasomes to produce IL-1 β in macrophages and promoted chemokine signaling (23). A recent study showed that uric acid was increased in the serum and liver of alcohol-fed mice. Depletion of uric acid with allopurinol provided significant protection from alcohol-induced inflammatory response, steatosis and liver damage (24). Other clinical studies have also demonstrated that lowering uric acid benefited inflammation, endothelial function, blood pressure and insulin resistance (25-27). These studies demonstrated that uric acid induced an inflammatory response and inflammatory cell infiltration in numerous ways. The study by Petta *et al* (12) in Italy showed similar results, indicating that hyperuricemia was independently associated with lobular inflammation. Despite a small sample size, the present study was similar to that of Petta *et al* (12), representing different ethnicities with similar findings. These results indicated that hyperuricemia has an important role in inducing inflammation. A cross-sectional study, such as the present study, cannot definitively confirm whether hyperuricemia was a cause or a marker of hepatic necroinflammation. However, it was a valuable marker of hepatic necrosis.

In a clinical cohort study, Afzali *et al* (28) found that the SUA level was associated with the development of cirrhosis. However, the present study showed that hyperuricemia was not associated with advanced fibrosis in NAFLD; the study populations were different. The present subjects were patients with biopsy-proven NAFLD in China. The patients in the study by Afzali *et al* included different ethnicities and liver diseases, with varied etiopathogeneses. Hyperuricemia is significantly associated with NAFLD (6-8). However, SUA was normal in

a number of patients with NAFLD, which indicated that SUA mediated the pathogenesis of NAFLD, but in conjunction with other factors. The present results revealed no association between hyperuricemia and advanced fibrosis of NAFLD. However, SUA levels were associated with greater severity of lobular inflammation and NASH. Others studies demonstrated that uric acid induced inflammation and inflammatory cell infiltration in a variety of ways (25-27). Repeated inflammation leads to liver fibrosis suggesting that hyperuricemia was indirectly involved in liver fibrosis. The present cross-sectional study did not confirm the causal association between hyperuricemia and liver fibrosis. Additional prospective studies are required to provide evidence linking hyperuricemia with liver fibrosis.

The limitations of the present study are associated with the cross-sectional design, which cannot determine any causality between uric acid levels and NAFLD histology. In addition, the interpretation of the results may be affected by the small sample size. Further studies are required to reveal the detailed association and possible mechanisms underlying the association between SUA and NAFLD.

In conclusion, the SUA level is significantly associated with the degree of steatosis. Hyperuricemia is associated with a greater severity of lobular inflammation and higher NAS. Hyperuricemia was independently associated with greater odds of advanced lobular inflammation of NAFLD. In the future, large-scale studies are required to develop novel therapeutic targets and intervention strategies for NAFLD.

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