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Serum uric acid and non-alcoholic fatty liver disease in non-hypertensive chinese adults: the cardiometabolic risk in chinese (CRC) study

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Abstract. – OBJECTIVE: The causal relationship between serum uric acid (SUA) level and non-alcoholic fatty liver disease (NAFLD) has not yet been clarified. The objective of the study was to determine the association between SUA and NAFLD, as well as assess the interactions between SUA and other metabolic risk factors regarding NAFLD.

PATIENTS AND METHODS: The study samples related to a community-based health examination survey conducted in Central China. Initially, a total of 24,878 patients with medical examination were included. After excluding the individuals with confounding factors, the remaining 21,798 subjects with biomarkers available were included in the present study.

RESULTS: The data show that the risk of NAFLD significantly increased with the elevated SUA levels. Further adjustments for sex, age, and other confounding metabolic factors did not change the increasing trend of NAFLD risk. The odds ratios [ORs, 95% confidence interval (CI)] of NAFLD across the increasing quintiles of SUA were 1.00, 1,530 (1.174-1.995), 2.24 (1.714-2.886), 2.636 (2.019-3.441), and 3.714 (2.828-4.877) (*p* for trend < 0.0001). Also, significant interaction was found between SUA and prehypertension in relation to the NAFLD risk (*p* for interaction < 0.05).

CONCLUSIONS: SUA was significantly associated with NAFLD risk, independent of other metabolic risk factors, and SUA also had significant interaction with prehypertension regarding the risk of NAFLD.

Key Words:
Serum uric acid, Non-Alcoholic Fatty Liver Disease, Chinese adults, Cardiometabolic risk factors, Prehypertension.

Introduction

Non-alcoholic fatty liver disease (NAFLD), the manifestations of which range from simple steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis, is the result of hepatic fat accumulation in patients without a history of excessive alcohol consumption[1]. NAFLD affects approximately 20-30% of the general population and the prevalence is rising worldwide, which is recognized as a major cause of liver-related morbidity and mortality[2]. NAFLD is commonly associated with obesity, type 2 diabetes mellitus, dyslipidemia and hypertension, which form a cluster of metabolic abnormalities identified as metabolic syndrome (MetS)[3]. Therefore, NAFLD has also been regarded as a hepatic manifestation of MetS[4]. Similar to NAFLD, serum uric acid (SUA), the end product of purine metabolism by liver[5], also has been linked to both MetS and cardiovascular disease[1,2,6]. Several previous studies indicated that the elevated SUA associated with the development or progression of NAFLD in European or Korean populations[7-10].

Due to lack of evidence, the precise role of SUA in the development of NAFLD remains unclear in the adults from Central Chinese population. Therefore, the aim of this study was to determine the associations between SUA levels and the risk of ultrasound-defined NAFLD in a large population sample of the Chinese with normal range of blood pressure (SBP < 140 mmHg and DBP < 90 mmHg), dwelling in central region of the country. We particularly assessed the interactions between SUA and other metabolic risk factors in relation to NAFLD.

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Patients and Methods

Study Population

All individuals, who were randomly selected from the residents living in the urban area of Xuzhou, central China, participated in a community-based health examination survey. Written informed consent was obtained from each participant before inclusion in the study. The study was reviewed and approved by the Ethics Committee of the Central Hospital of Xuzhou, Affiliated Hospital of Medical School of Southeast University. Initially 24,878 individuals were identified, all of whom were subjected to a complete medical examination, a clinical consultation, and blood laboratory tests. All individuals provided demographic details, medical history, and information regarding the use of medication at the time of their clinical consultation.

From these participants, we excluded 624 potential patients of hypertension (SBP ≥ 140 mmHg and DBP ≥ 90 mmHg) and 521 individuals were excluded for having coronary heart disease, hyperthyroidism, rheumatoid arthritis, cancer, or for taking any kind of medication within four weeks, or with impaired hepatic and renal function. Individuals were also excluded due to having incomplete data regarding ultrasonography (n=125) or blood test results (n= 328), or for having positive hepatitis B surface antigen (n=348) and hepatic C antibody (n=8). In addition, 1126 individuals were also excluded for reporting daily alcohol intake of at least 40 g and 5 times per week. Thus, finally 21,798 eligible individuals were enrolled in the study. There was no significant difference in the clinical characteristics between the study participants and those who were excluded.

Anthropometry

Height was measured to the nearest 0.5 cm without shoes and body weight was measured to the nearest 100 g, without shoes on. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Blood pressure was measured with a standard mercury sphygmomanometer three times consecutively after the participant had rested for at least 5min. With the arm placed at the heart level, three measurements, 60s apart, were taken. We used the average of the three readings for each individual regarding systolic blood pressure (SBP) and diastolic blood pressure (DBP) data analysis.

Assessment of Biomarkers and Covariates

Fasting blood samples were collected for measurement of SUA, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), aspartate aminotransferase (AST) and alanine transaminase (ALT). For this purpose, peripheral blood sample from each individual was drawn following an overnight (8-12h) fasting. After collection, blood was transferred to glass tube and allowed to clot at room temperature. Immediately following clotting, serum was separated by centrifugation at 3000 rpm for 15 min. All biochemical assays were performed enzymatically using an auto analyzer (Type 7600, Hitachi Ltd, and Tokyo, Japan). Questionnaires were used to determine the alcohol consumption (both quantity and frequency) and g of alcohol consumption were calculated by multiplying frequency with amount.

Disease Definition

NAFLD was diagnosed based on abdominal ultrasound without including alcohol consumption, viral, or autoimmune liver disease[8]. The diagnosis of fatty liver was based on the findings of abdominal ultrasonography using a portable ultrasound device (GE, LOGIQe, 5.0-MHz transducer, USA) and included the presence of increased liver echogenicity (bright), with stronger echoes in the hepatic parenchyma than in the renal parenchyma, vessel blurring and narrowing of the lumen of the hepatic veins[11,12]. Prehypertension was defined as SBP between 120-139 mmHg or DBP between 80-89 mmHg as per guidelines of The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7)[13].

Statistical Analysis

The data were represented as mean±standard error (SE) and group comparisons were made using general linear models analysis of variance (ANOVA). TG, AST, and ALT were logarithmically transformed to improve the normality. We used logistic regression in estimating the odds ratios (ORs) for NAFLD risk, adjusting for covariates including age, sex, BMI, SBP, DBP, and biomarkers. The interactions between SUA and other factors were assessed using likelihood ratio test (LRT), with a comparison of the log likelihood of the two models with and without the interaction terms. All reported *p*-values were two-

Table I. Baseline characteristics with respect to serum uric acid (SUA) levels.

Variable	SUA (Quintiles) (μmol/L)					*p* for trend
	Q1 (SUA < 223.7)	Q2 (223.7 < SUA < 267.0)	Q3 (267.0 < SUA < 311.6)	Q4 (311.6 < SUA < 363.6)	Q5 (SUA > 363.6)	
Number (N)	4356	4367	4361	4356	4358	
Age (years)	40.49 ±10.59	41.74 ± 12.15	42.22 ± 12.48	41.25 ± 12.59	40.04 ± 12.05	0.064
BMI (kg/m^2)	22.18 ± 2.67	22.90 ± 2.95	23.73 ± 3.06	24.53 ± 3.04	25.54 ± 3.04	< 0.001
Height (cm)	161.83 ± 6.25	163.68 ± 7.27	167.48 ± 8.00	170.47 ± 7.37	172.33 ± 6.39	< 0.001
SBP (mmHg)	114.42 ± 10.95	116.01 ± 11.32	118.32 ± 10.55	120.13 ± 9.62	121.74 ± 8.92	< 0.001
DBP (mmHg)	73.33 ± 7.14	74.45 ± 7.27	76.26 ± 6.75	77.48 ± 6.33	78.61 ± 5.78	< 0.001
FBG (mmol/L)	5.16 ± 1.11	5.24 ± 1.15	5.31 ± 1.16	5.32 ± 1.02	5.29 ± 0.80	< 0.001
HDL (mmol/L)	1.47 ± 0.32	1.42 ± 0.31	1.31 ± 0.31	1.24 ± 0.30	1.18 ± 0.28	< 0.001
LDL (mmol/L)	2.71 ± 0.74	2.91 ± 0.80	3.01 ± 0.80	3.10 ± 0.80	3.18 ± 0.82	< 0.001
logTG	-0.08 ± 0.21	-0.01 ± 0.24	0.07 ± 0.25	0.13 ± 0.26	0.23 ± 0.26	< 0.001
TC (mmol/L)	4.45 ± 0.83	4.60 ± 0.88	4.67 ± 0.92	4.71 ± 0.89	4.84 ± 0.93	< 0.001
logAST	1.23 ± 0.12	1.26 ± 0.13	1.28 ± 0.14	1.30 ± 0.13	1.33 ± 0.14	< 0.001
logALT	1.17 ± 0.21	1.23 ± 0.22	1.29 ± 0.23	1.35 ± 0.22	1.43 ± 0.24	< 0.001

Abbreviations: BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TG: triglyceride; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

sided and variables with *p*-values of < 0.05 were considered statistically significant. The SAS software (SAS, Version 9.0; SAS Institute Inc., Cary, NC, USA) was used for statistical analyses.

Results

Baseline Characteristics with Respect to SUA Levels

The study participants were divided into five groups according to their SUA levels (in quintiles). The subjects had a mean age of 41.1 (range: 18-90) years and a mean BMI of 23.73 kg/m^2. The mean SBP was 118 (range: 78-139) mmHg and DBP was 75 (range: 49-89) mmHg. Baseline characteristics of the study participants as per quintile of SUA are shown in Table I. Individuals with high SUA levels had higher SBP, DBP, BMI, TC, TG, and LDL-C, but lower HDL-C.

Association Between SUA Level and NAFLD

Among the 21,798 participants, the prevalence of NAFLD was 23.35% (n=5091). The associations between SUA levels and risk of NAFLD are shown in Table II. The ORs for NAFLD substantially increased with increasing concentrations of SUA ($p < 0.0001$). In the model adjusting for sex and age (Model 1), the OR for NAFLD, comparing the highest with the lowest SUA quartile, was 11.159 (95% CI 9.492-13.119). Further adjust-

Table II. Association between SUA and NALFD.

Parameter	Normal	NALFD	Model 1		Model 2		Model 3	
			OR	95% CI	OR	95% CI	OR	95% CI
Q1	4112 (94.4%)	244 (5.6%)	1	1	1	1	1	1
Q2	3822 (87.5%)	545 (12.5%)	2.14	1.83-2.52	1.64	1.37-1.95	1.53	1.17-1.99
Q3	3440 (78.9%)	921 (21.1%)	3.54	3.03-4.14	2.31	1.95-2.76	2.22	1.71-2.89
Q4	3004 (69.0%)	1352 (31.0%)	5.67	4.83-6.65	3.15	2.64-3.76	2.64	2.02-3.44
Q5	2329 (53.4%)	2029 (46.6%)	11.16	9.49-13.12	4.76	3.98-5.67	3.71	2.83-4.88
p for trend			< 0.001		< 0.001		< 0.001	

Abbreviations: SUA: serum uric acid; NAFLD: nonalcoholic fatty liver disease. Model 1: adjusted sex, age; Model 2: adjusted sex, age, BMI, SBP, DBP; Model 3: adjusted sex, age, BMI, SBP, DBP, TC, HDL-C, LDL-C, Log TG, Log AST, Log ALT.

ment for BMI, SBP, and DBP (Model 2) substantially attenuated the magnitude of the ORs for NAFLD, but did not affect the statistical significance. Using the lowest SUA quintiles as reference, the ORs of NAFLD [95% CI] across increasing quintiles of SUA were 1.00, 1.530 (1.174-1.995), 2.24 (1.714-2.886), 2.636 (2.019-3.441), and 3.714 (2.828-4.877), respectively (p for trend < 0.001), after further adjustment for TC, HDL-C, LDL-C, LogTG, LogAST, LogALT (Model 3).

Associations Bbetween SUA and NAFLD with Respect to Age, BMI, and Biomarkers

We also assessed the interactions between SUA and metabolic factors (Table III). In order for performing stratified analyses, we grouped fasting blood glucose (FBG) and LDL into three categories (tertiles) i.e. low, medium, and high levels. Associations between SUA and NAFLD were found to be non-significant by sex, age, BMI, FBG and LDL (all p-values for interaction > 0.05). The interactions between SUA and prehypertension was significant in relation to NAFLD risk (p for interaction = 0.004). The associations between SUA and NAFLD were also significant in the group with prehypertension.

Discussion

In clinical and epidemiological studies, SUA has been found to be positively related to the risk of cardiovascular disease and MetS[1,2,6]. Although, several studies suggested a relationship between SUA and NAFLD[1,2,6-10], the data were collected from relatively small sample sizes and were limited to European or Korean populations. Most of these studies[2,8,9] also included the individuals with hypertension which is suspected to have directly influenced both SUA and NAFLD. Besides, not all studies were in agreement on the relationship between SUA and NAFLD[4,14,15]. In the present study, we found strong positive associations between elevated SUA levels and NAFLD risk in the non-hypertension Chinese adults, independent of other metabolic changes, which also substantiates the previous findings interlinking SUA levels and NAFLD risk[1,2,8,9]. The link between SUA and NAFLD may relate to several underlying mechanisms. SUA has been associated with hypertension, obesity, hypertriglyceridemia and hyperglycemia[16], all of which are important components of MetS. In addition, SUA has been also associated with the MetS and cardiovascular disease[1,2,6], which plays an important role in the development or progression of NAFLD[2,4]. Alternatively, the relationship between SUA and NAFLD can possibly be confounded by the presence of MetS. In support of this reasoning, it is the hyperinsulinemia that induces hyperuricemia by reducing urinary excretion of uric acid[17], and that the oxidative stress can result in the hyperuricemia seen in MetS[18]. However, it was also suggested that the elevated SUA level was independently associated with NAFLD risk, regardless of insulin resistance, components of MetS, and indices of liver and kidney function[19].

NAFLD has been suggested to represent the aftermath of two distinct steps of hepatic insults i.e. the "two-hit" theory of NAFLD[20]. In this regard, liver fat accumulation is the 'first hit', and the impaired hepatic lipid metabolism results in the development of hepatic steatosis; whereas the 'second hit' kicks in as steatotic liver subsequently becomes vulnerable to the inflammatory process including oxidative stress, peroxidation, and inflammatory cytokines/chemokines. Of note, SUA has been also shown to act as an intracellular pro-oxidant to exert the pro-inflammatory and pro-oxidant effects in the adipose tissue[21,22]. Thus, SUA can play a pathogenic role in the development of NAFLD, as the increased SUA accumulation leads to inflammatory and oxidative perturbations, independently from MetS[22,23].

In addition, we found a significant interaction between SUA and prehypertension in relation to NAFLD risk. SUA and prehypertension showed an additive effect in enhancing the risk of NAFLD. For most patients, prehypertension is not a disease but, rather, one of many risk factors for the development of certain diseases, such as diabetes, insulin resistance, MetS, and cardiovascular diseases[24,25]. The animal models[26] and prospective studies in humans[27,28] both confirmed that SUA levels were significantly associated with the progression of elevated BP. Two main mechanisms are suggested to account for a link between SUA and BP. First, SUA may lead to renal vasoconstriction and an increase in systemic BP through inhibition of the nitric oxide synthesis[29]. Second, SUA may directly activate the renin–angiotensin system, which leads to an increase in the expression of angiotensin II and angiotensinogen, subsequently giving rise to increased tubular reabsorption of SUA[30]. As an additional mechanism, SUA can also induce in-

Table III. Stratified associations between serum uric acid (SUA) and NAFLD with respect to age, BMI, and biomarkers.

Variable		SUA (Quintiles) (μmol/L)					*p* for trend	*p* for interaction
		Q1 (SUA < 223.7)	Q2 (223.7 < SUA < 267.0)	Q3 (267.0 < SUA < 311.6)	Q4 (311.6 < SUA < 363.6)	Q5 (SUA > 363.6)		
Sex	Female	1	1.67 (1.22-2.29)	2.38 (1.70-3.32)	3.85 (2.61-5.70)	4.38 (2.46-7.80)	< 0.001	0.162
	Male	1	1.371 (0.82-2.29)	1.92 (1.19-3.09)	2.125 (1.33-3.40)	3.09 (1.93-4.94)	< 0.001	
Age (years)	< 60	1	1.60 (1.21-2.13)	2.33 (1.76-3.09)	2.63 (1.97-3.51)	3.68 (2.74-4.94)	< 0.001	0.188
	≥ 60	1	1.22 (0.59-2.53)	1.81 (0.89-3.71)	2.89 (1.40-5.97)	3.99 (1.88-8.53)	< 0.001	
BMI (Kg/m2)	< 28	1	1.78 (1.35-2.34)	2.63 (2.01-3.46)	3.31 (2.49-4.380)	4.81 (3.60-6.42)	< 0.001	0.103
	≥ 28	1	1.34 (0.66-2.74)	2.06 (1.02-4.15)	3.59 (1.80-7.17)	4.67 (2.33-9.36)	< 0.001	
FBG (mmol/L)	Q1	1	1.36 (0.78-2.39)	2.30 (1.34-3.94)	2.23 (1.267-3.94)	3.45 (1.93-6.16)	< 0.001	0.265
	Q2	1	1.51 (0.90-2.52)	2.37 (1.44-3.90)	3.30 (1.98-5.47)	4.15 (2.48-6.96)	< 0.001	
	Q3	1	1.38 (0.96-1.99)	1.62 (1.13-2.32)	1.80 (1.25-2.60)	2.49 (1.71-3.61)	< 0.001	
Prehypertension	Yes	1	1.55 (1.14-2.11)	2.17 (1.60-2.94)	2.47 (1.82-3.37)	3.48 (2.55-4.76)	< 0.001	0.004
	No	1	1.42 (0.84-2.39)	2.44 (1.47-4.06	3.50 (2.04-6.00)	5.07 (2.86-8.99)	< 0.001	
LDL (mmol/L)	Q1	1	1.73 (1.04-2.89)	2.26 (1.34-3.82)	3.08 (1.78-5.32)	4.25 (2.43-7.43)	< 0.001	0.105
	Q2	1	1.88 (1.15-3.06)	2.97 (1.86-4.75)	3.18 (1.95-5.18)	5.02 (3.06-8.23)	< 0.001	
	Q3	1	1.27 (0.85-1.91)	1.80 (1.22-2.68)	2.15 (1.45-3.20)	2.85 (1.89-4.28)	< 0.001	

Abbreviations: BMI: body mass index; HDL-C: high-density lipoprotein cholesterol. Analyses were adjusted for covariates age, BMI, sex, and biomarkers when they were not the strata variables.

flammation, vascular smooth muscle cell proliferation, and oxidative stress, which may lead to irreversible damage to small renal vessels, resulting in renal microvascular lesions as well as elevated BP[31,32]. It was shown that prehypertension, especially high SBP was associated with a greater risk of NAFLD[33]. Moreover, through its ability to interfere with some actions of insulin by reducing endothelial nitric oxide[34], SUA might contribute to the development of insulin resistance which was suggested to play a role in the association between BP and NAFLD[35]. Due to the cumulative effect of more than one risk factors involved in individuals with high SUA levels, BP should be monitored regularly in addition to lifestyle changes including diet, physical activity and alcohol consumption.

Whereas a major strength of our study is the large sample size that ensures sufficient impact of the complex interactions between SUA and other cardiometabolic factors, certain limitations however also need to be considered. First, this was a cross-sectional study that does not allow us to determine any causality between SUA and NAFLD. To confirm that the associations between SUA and NAFLD are independent of other metabolic risk factors, a prospective study is needed. Second, the study population belonged to a specific geographic location and, therefore, the results may not be applicable to the general population in China. Third, NAFLD diagnosis was based on ultrasonographic findings, which is less sensitive than biopsy to detect mild steatosis; however, this method is clinically acceptable and is widely used in epidemiological studies of NAFLD for being non-invasive, safe, easy to perform and widely available.

Conclusions

This study has shown significant associations between SUA levels and NAFLD risk in the Chinese adults, independent of other metabolic risk factors. We observed significant interactions between SUA status and prehypertension with regard to NAFLD risk. The effects of SUA and prehypertension on NAFLD were additive. Furthermore, prospective studies will be required to confirm the causality of the associations which will not only broaden our comprehension of the NAFLD mechanisms, but also assist in the eventual development of new prevention and treatment strategies for the disease.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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