Elevated serum uric acid is an independent risk factor for nonalcoholic fatty liver disease in Japanese undergoing a health checkup

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Abstract

Background and study aims : The question of whether elevated serum uric acid is an independent risk factor for nonalcoholic fatty liver disease evident on ultrasonography was investigated by longitudinal approach in Japanese undergoing a health checkup.

Patients and methods : A total of 1,386 male and 3,453 female nondrinkers participating in health checkups in both 2000 and 2005 were included. Multiple logistic regression analyses were performed for 1,042 men (51.4 ± 11.2 years old) and 3,076 women (51.8 ± 9.2 years old) to identify independent factors for newly developed nonalcoholic fatty liver disease in 2005. Adjustment was made for age, body mass index, body mass index increase for 5 years, systolic blood pressure, triglyceridemia, fasting blood glucose, and smoking.

Results: The prevalence of nonalcoholic fatty liver disease and body mass index, systolic blood pressure, and triglyceride were significantly higher in the participants with elevated serum uric acid, with a significant increasing trend in relation to serum uric acid quartiles. Nonalcoholic fatty liver disease was newly diagnosed in 17.4% of males and 8.2% of females, respectively, in 2005. Serum uric acid adjusted for other factors was a risk factor for nonalcoholic fatty liver disease in both sexes and quartiles 3 and 4 had significantly elevated risks. The odds ratio and 95% confidence interval for one increment of serum uric acid were 1.31 and 1.11-1.56 in men and 1.30 and 1.10-1.53 in women, respectively.

Conclusions : Elevated serum uric acid is an independent risk factor for nonalcoholic fatty liver disease in Japanese undergoing a health checkup. (Acta gastroenterol. belg., **2010**, 73, **12-17**).

Key Words : uric acid, nonalcoholic fatty liver disease, risk factor, health checkup.

Abbreviations : Nonalcoholic fatty liver disease, NAFLD ; body mass index, BMI ; triglyceride, TG ; fasting blood glucose, FBG ; odds ratio, OR ; 95% confidence interval, CI ; nonalcoholic steatohepatitis, NASH.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is now generally increasing due to consumption of a high fat and calorie diet and a sedentary life style and has attained a prevalence of 15-25% in many countries (1). NAFLD is closely associated with the metabolic syndrome, the most common cause of liver function abnormality in the clinical setting, and the most frequently demonstrable condition by ultrasonography at health checkups (2-5). It comprises a wide spectrum of histologic alterations, ranging from steatosis, through steatohepatitis and fibrosis to cirrhosis (1,6). It is well accepted that increased insulin resistance may be closely related to fat accumulation in hepatocytes.

The metabolic syndrome is defined as the clustering of several cardiovascular risk factors, including visceral adiposity (large waist circumference), dyslipidemia, hypertension, and impaired fasting glucose (7-9). Since both NAFLD and the metabolic syndrome are closely associated with insulin resistance, the liver changes are considered as a hepatic consequence of the metabolic syndrome (2,7-9).

Many investigations have demonstrated that elevated serum uric acid levels are often present with obesity, hypertension, hyperlipidemia, and glucose intolerance (10-14). Hyperuricemia is also reported to be closely associated with insulin resistance, with potential as an independent predictor of cardiovascular disease (11,13-17). Since elevated serum uric acid levels are closely associated with visceral obesity as well as insulin resistance, it seems likely that a link may also exist with NAFLD.

Although one study demonstrated that obesity was the only independent factor for NAFLD, the majority of investigations have revealed that elevated serum uric acid is associated with NAFLD in cross-sectional approaches (18-23). Therefore, the present longitudinal investigation was performed to demonstrate a causal relationship between elevated serum uric acid and NAFLD assessed by ultrasonography. Adjustment was made for age, body mass index (BMI), BMI increase for 5 years, systolic blood pressure, triglyceride (TG), fasting blood glucose (FBG), and smoking status in Japanese undergoing a health checkup.

Methods

Design of the study

This study was a retrospective longitudinal analysis of apparently healthy Japanese undergoing a health checkup.

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Subjects of the longitudinal study

The participants voluntarily underwent annual health checkups at Okazaki City Medical Association, Public Health Center between 2000 and 2005. The participants also voluntarily selected the examinations including blood chemistry and abdominal ultrasonography.

The numbers of participants undergoing medical checkups, including ultrasonograpy, in 2000 and 2005 were 26,247 (men : 14,627 and women : 11,620) and 32,548 (men : 17,207 and women : 15,341), respectively. After exclusion of participants who had past or present histories of hepatic diseases induced by drugs, autoimmune, and unknown etiology based on questionnaire and positive results of hepatitis virus, a total of 12,453 participants who underwent health checkups in both 2000 and 2005 [men : 6,924 (49.5 ± 10.5 years old), women : 5,529 (50.7 ± 9.3 years old)] were included. Non drinkers assessed according to a self-administered questionnaire, 4,839 [men 1,386 (51.0 ± 11.0 years old), women 3,453 (52.1 ± 9.2 years old)] were finally included for the analysis.

A total of 721 cases (men 344 ; 24.8%, women 377; 10.9%) in 4,839 nondrinkers (men 1,386, women 3,453) were assessed as having NAFLD on ultrasonography in 2000. A total of 4,118 participants [men 1,042 (51.4 ± 11.2 years old) and women : 3,076 (51.8 ± 9.2 years old)] without NAFLD in 2000 were longitudinally analyzed to determine the risk factors for newly developing NAFLD in 2005.

Questionnaire

Subjects provided data for alcohol drinking habits and smoking status through a self-administered questionnaire which was checked during individual interview by expert nurses in the center. Alcohol drinking habits were classified into none, occasional, and daily. Non drinkers were selected according to these answers.

Measurements

Age was categorized into four groups. Body weight was measured, in light clothing, to the nearest 0.1 kg and height to the nearest 0.1 cm. BMI was calculated as weight (kg) divided by height (m) squared and divided into five categories using modified criteria by reference to those reported by the Japan Society for the Study of Obesity. Blood pressure was measured to the nearest 1 mmHg by automatic sphygmomanometry (BP-203 RV III B, Nippon COLIN, Komaki, Japan).

Blood samples were taken from each participant after overnight fasting. Uric acid, TG, and FBG were measured with Hitachi autoanalyzer models 7600 and 7700 (Hitachi Medical, Co., Tokyo, Japan).

We found that 216/1,170 (18.5%) men and 26/3,453 (0.8%) women were diagnosed with hyperuricemia (serum uric acid ≥ 7.0 mg/dL) according to the criteria of the Japan Society of Gout and Nucleic Acid Metabolism. The mean serum uric acid significantly differed between men and women (men 5.77 ± 1.20 mg/dL and women 4.31 ± 0.93 mg/dL, $p < 0.001$). Therefore, sex-specific quartiles of uric acid were determined as reported previously (12). Quartiles 1 to 4 for men were < 5.00 mg/dL, 5.00-5.69 mg/dL, 5.70-6.49 mg/dL, and ≥ 6.50 mg/dL. For women they were < 3.70 mg/dL, 3.70-4.29 mg/dL, 4.30-4.89 mg/dL, and ≥ 4.90 mg/dL, respectively. The numbers in these groups were respectively 331, 328, 351, and 376 for men and 796, 922, 867, and 868 for women.

Abdominal ultrasonographic examination was performed using convex-type real-time electronic scanners (SSA 250 and 300, Toshiba Medical, Co., Tokyo, Japan) by ten technicians lacking any information about the subjects. All images were printed on sonograph paper and reviewed by other technicians and six gastroenterologists who were educated about the criteria for NAFLD diagnosis listed below. NAFLD was assessed according to the modified criteria reported previously (5,24,25). Briefly, it was assessed when the difference of liver and renal cortical echo amplitudes was more than 10 and otherwise both attenuation of echo penetration and decreased visualization of veins in the liver were observed.

Statistical Analyses

For each quartile of serum uric acid, the risk of NAFLD was calculated for men and women separately. Logistic regression analyses were followed to estimate the odds ratio (OR) and 95% confidence interval (95% CI) for the association of newly assessed NAFLD in 2005 with the serum uric acid concentration measured in 2000. We used two models in both sexes ; one age-adjusted and the other multivariate model with adjustment for age (< 40, 40-49, 50-59, and ≥ 60), BMI (< 18.50 kg/m^2, 18.50-22.00 kg/m^2, 22.01-25.00 kg/m^2, 25.01-29.99 kg/m^2, and ≥ 30.00 kg/m^2), BMI increase for 5 years, smoking status (never, ever, or unknown), systolic blood pressure, TG, and FBG. To test for linear trends, similar analyses based on the concentration of uric acid were performed with adjustment for the potential confounders listed above. *P* values were two-sided, with less than 0.05 indicating statistical significance. Analyses were performed using computer soft ware (SPSS version 13.0 for Windows).

Informed Consent

Informed consent was obtained from all participants.

Results

Table 1 summarizes data for the clinical characteristics of the participants according to sex-specific serum uric acid quartiles in 2000. A trend for increasing serum con-

Table 1. — **Baseline clinical characteristics of the participants according to serum uric acid quartiles**

		Serum uric acid quartiles				
	Overall	**Quartile 1**	**Quartile 2**	**Quartile 3**	**Quartile 4**	**p values**
Men						
Uric acid range (mg/dL)		< 5.00	5.00 - 5.69	5.70 - 6.49	≥ 6.50	
Number	1,386	331	328	351	376	
Age	51.0 ± 11.0	52.3 ± 10.4	50.4 ± 10.3	50.2 ± 11.5	51.1 ± 11.4	0.051
BMI (kg/m^2)	23.0 ± 3.0	21.8 ± 2.6	22.4 ± 2.6	22.3 ± 2.8	24.4 ± 3.2	< 0.001
BMI increase for 5 years (kg/m^2)	0.06 ± 1.17	0.11 ± 1.14	0.14 ± 1.20	0.07 ± 1.16	-0.06 ± 1.18	0.100
Systolic blood pressure (mmHg)	118.0 ± 17.4	114.7 ± 16.0	116.3 ± 17.4	117.9 ± 16.6	122.4 ± 18.3	< 0.001
FBG (mg/dL)	96.2 ± 9.7	95.5 ± 10.6	95.6 ± 9.6	96.6 ± 9.6	96.8 ± 9.7	0.195
TG (mg/dL)	123.9 ± 66.0	109.2 ± 55.6	112.0 ± 55.1	127.5 ± 70.6	143.8 ± 73.0	< 0.001
Smoker (%)	38.5	44.1	43.3	35.6	31.9	0.007
NAFLD (%)	24.8	11.5	18.0	25.4	42.0	< 0.001
Women						
Uric acid range (mg/dL)		< 3.70	3.70 - 4.29	4.30 - 4.89	≥ 4.90	
Number	3,453	796	922	867	868	
Age	52.1 ± 9.2	49.3 ± 8.9	50.8 ± 9.1	53.0 ± 9.0	55.1 ± 8.6	< 0.001
BMI (kg/m^2)	22.2 ± 2.9	21.4 ± 2.6	21.8 ± 2.7	22.3 ± 2.8	23.4 ± 3.1	< 0.001
BMI increase for 5 years (kg/m^2)	-0.09 ± 1.19	-0.05 ± 1.12	-0.12 ± 1.17	-0.01 ± 1.21	-0.16 ± 1.28	0.056
Systolic blood pressure (mmHg)	116.7 ± 17.6	113.1 ± 16.2	115.2 ± 16.5	117.1 ± 18.2	121.4 ± 18.3	< 0.001
FBG (mg/dL)	92.6 ± 8.7	91.2 ± 8.3	91.7 ± 8.0	92.5 ± 8.3	94.8 ± 9.6	< 0.001
TG (mg/dL)	90.7 ± 51.1	79.2 ± 51.3	83.4 ± 40.5	90.8 ± 45.8	108.8 ± 60.3	< 0.001
Smoker (%)	4.4	5.3	4.3	4.0	3.9	0.867
NAFLD (%)	10.9	3.3	5.6	11.0	23.5	< 0.001

BMI : body mass index ; FBG : fasting blood glucose ; TG : trigliceridemia ; NAFLD : non-alcoholic fatty liver disease.

centration of uric acid with age was observed in women, whereas a marginal decreasing trend was observed in men. BMI was largest in the higher quartiles of men and women, and a 2 kg/m^2 larger BMI was more frequently observed in the highest quartile compared to the lowest. Consistent increases were also observed with the systolic blood pressure and TG in both sexes. In contrast, FBG was increased significantly only in women with high uric acid quartiles. A tendency for decrease in smokers was observed only in men. In addition, the prevalence of NAFLD in 2000 was much higher in the participants with a higher serum uric acid i.e., four times in men (42.0% versus 11.5%) and seven times in women (23.5% versus 3.3%) comparing the highest quartile to the lowest.

In 2005, 17.4% of men and 8.2% of women were newly diagnosed as having NAFLD. The risk linearly increased with the uric acid quartiles i.e., 9.9%, 11.2%, 22.5%, and 24.3% in men, and 4.9%, 6.2%, 9.8%, and 12.5% in women, respectively (Table 2).

Multiple logistic regression analysis revealed the serum uric acid concentration to be a risk factor for NAFLD in both sexes after adjustment for potential confounders, including age, BMI, BMI increase for 5 years, systolic blood pressure, TG, FBG, and smoking status (Table 2). Those in serum uric acid quartiles 3 and 4 had significantly increased risks as compared to quartile 1 in both sexes (men OR 2.18, 95% CI 1.29-3.71 and OR 2.31, 95% CI 1.34-4.01 and women OR 1.73, 95% CI 1.17-2.84 and OR 1.82, 95% CI 1.17-2.84, respectively). Linear trends were highly significant ($p < 0.001$ for men and women) and the ORs (95% CI) for one increment of serum uric acid were 1.31 (1.11-1.56) in men and 1.30 (1.10-1.53) in women.

Discussion

The present study demonstrated that elevated serum uric acid is an independent risk factor for NAFLD as assessed by ultrasonography in Japanese undergoing a health checkup. Multiple regression analysis confirmed that serum uric acid fully adjusted for other factors predisposed to NAFLD in both sexes.

It was demonstrated that serum uric acid was closely associated with various components contributing to metabolic syndrome. These include hypertension, visceral fat accumulation, and serum TG and FBG (11,12,26). It is also a risk factor for type 2 diabetes, myocardial infarction, stroke, and chronic kidney disease (13-16,27-29). Previous investigations also demonstrated a positive relationship between serum uric acid and NAFLD (19-

Table 2. — **The prevalence of newly diagnosed nonalcoholic fatty liver disease (NAFLD) in 2005 and multiple logistic regresseion analysis for NAFLD**

		NAFLD (%)	Age-adjusted OR*	95% CI	Multivariate OR**	95% CI
Men						
Serum uric acid	Quartile 1	9.9	1.00	Reference	1.00	Reference
	Quartile 2	11.2	1.09	0.63- 1.88	1.07	0.61- 1.89
	Quartile 3	22.5	2.69	1.65- 4.38	2.18	1.29- 3.71
	Quartile 4	24.3	3.05	1.85- 5.02	2.31	1.34- 4.01
Women						
Serum uric acid	Quartile 1	4.9	1.00	Reference	1.00	Reference
	Quartile 2	6.2	1.32	0.86- 2.03	1.21	0.77- 1.91
	Quartile 3	9.8	2.27	1.51- 3.42	1.73	1.12- 2.67
	Quartile 4	12.5	3.09	2.05- 4.66	1.82	1.17- 2.84

* : adjusted for age
** : adjusted for age, BMI, BMI increase for 5 years, systolic blood pressure, triglyceride, fasting blood glucose, and smoling status.

23). Since they were performed in a cross-sectional manner, they could not provide a direct evidence of a causal relationship between elevated serum uric acid and development of NAFLD. In contrast, we here demonstrated links in both sexes of Japanese on a longitudinal basis using subjects undergoing health checkups.

The Japan Society of Gout and Nucleic Acid Metabolism has defined hyperuricemia as a serum uric acid ≥ 7.0 mg/dL in both sexes. However, we found that 18.5% of male but only 0.8% of female participants was diagnosed with hyperuricemia. Thus, sex-specific quartiles of uric acid were used for the categories in regression analyses as reported previously (12). Interestingly, quartiles 3 and 4 had significant increased risks for NAFLD as compared to quartile 1 in both sexes and the ORs were quite similar between the sexes, despite the differences in the ranges of the quartiles. Although the serum uric acid values in quartiles 2 and 3 in both sexes were within the normal range, according to the criteria of the Society, the related prevalence of NAFLD and the values for metabolic components, including BMI, systolic blood pressure, and TG, were higher than in quartile 1 in both sexes. Furthermore, serum uric acid was also a risk factor for NAFLD when assessed as a continuous value.

Mechanisms of association between elevated serum uric acid and insulin resistance have been reported previously. Hyperinsulinemia reduces the clearance of uric acid in the renal proximal tubule, resulting in an elevation of serum levels (30,31). Uric acid itself dose-dependently induces endothelial dysfunction by inhibiting nitric oxide (32,33). This then reinforces insulin resistance (34). Finally, uric acid has anti-oxidant properties (35), suggesting that it may counteract with the increased oxidants in the metabolic syndrome. Insulin resistance is recognized as an etiological factor for NAFLD (2,7-9). Thus, we speculate an involvement in its pathogenesis in subjects with elevated serum uric acid, although we did not actually measure insulin resistance in the present study. Taken together with the present data, even participants with slightly elevated serum uric acid within normal upper limit may have increased insulin resistance, which is closely related to development of NAFLD.

De novo increase in purine synthesis may be pathogenetically linked to hepatic fatty acid synthesis (36,37) and visceral fat obesity is known to be more closely linked to overproduction of uric acid and liver steatosis than subcutaneous fat obesity (33). Taking together the available findings, increased fatty acid synthesis and visceral fat in subjects with overproduction of uric acid may be closely linked to development of NAFLD.

Previous investigators extensively explored risk factors for NAFLD. Overproduction of glucose, VLDL, and coagulation factors, which significantly contribute to risk for cardiovascular disease, may occur based on insulin resistance in the metabolic syndrome and NAFLD (9,38,39). Although obesity is a well established risk factor for NAFLD, even lean subjects may develop NAFLD in the presence of insulin resistance, suggesting that it may be important to diagnose NAFLD, irrespective of obesity. It is widely accepted that NAFLD is closely associated with metabolic syndrome as well as cardiovascular disease (1,2,8-10,13,15,16). NAFLD may develop nonalcoholic steatohepatitis (NASH) which is clinically more important (40,41). Therefore, it is important to predict development of NAFLD in the asymptomatic participants undergoing health checkups. We analyzed the data of participants who voluntarily underwent ultrasonographic examination, which can readily estimate hepatic fatty acid accumulation. However, it is not

always available at health checkups. Therefore, we recommend that the serum uric acid level be measured routinely at future health checkups in order to assess the risk of development of NAFLD.

A major limitation of the present study was the retrospective longitudinal design. The subjects were limited to Japanese participants undergoing health checkups. The participants voluntarily underwent annual health checkups each year. Although it would have been preferable to follow up all participants in 2000 to investigate the risk factor for fatty liver in 2005 in a cohort manner, only 47.4% of the participants in 2000 received medical checkups in 2005. The frequencies and intervals of checkups were not assessed in the present study. We speculate that possible bias for selection of participants and undetermined frequencies and intervals may have weakened the present results. Furthermore, since insulin resistance was not included in the logistic regression analysis, we could not demonstrate how insulin resistance was involved in the relationship between elevated serum uric acid and development of NAFLD. In addition, we could not determine the origin of elevated serum uric acid since we did not have information regarding either detailed dietary patterns or urinary secretion of uric acid. Although histological diagnosis is more accurate, we had to rely on ultrasonography for the purposes of the present study. Ultrasonographic findings were reviewed by well educated gastroenterologists but diagnosis of NAFLD may have some variations. In addition, ultrasonography cannot distinguish between NAFLD and NASH. Therefore, the present finding has limited potential to diagnose NAFLD accurately and estimate the future prognosis of possible liver injury. However, ultrasonography has been widely used to assess fatty liver since it is a non-invasive procedure for screening purpose (3-5,7,21,42). The observed prevalence of fatty liver, 24.8% in men and 10.9% in women in the present study is consistent with values in previous Japanese reports (3,7,20).

In conclusion, elevated serum uric acid is an independent risk factor for NAFLD as assessed by ultrasonography in Japanese undergoing health checkups. The present findings cast a new light on clinical significance of elevated serum uric acid. We propose that participants with hyperuricemia should be advised to make changes in life-style to reduce serum uric acid and to prevent further development of NAFLD and metabolic disorders. However, future cohort studies assessing the influence of serum uric acid levels are still recommended to confirm and extend our present results.

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