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Serum uric acid levels predict incident nonalcoholic fatty liver disease in healthy Korean men

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Abstract

The objective of the study was to assess the prospective association between serum uric acid levels and incident nonalcoholic fatty liver disease in a cohort of healthy Korean men. A cohort study was performed on 5741 Korean men, 30 to 59 years of age, with no evidence of fatty liver disease on liver ultrasound and with no major risk factors for liver disease at baseline. Study participants were followed in annual or biennial health examinations between 2002 and 2008. The presence of fatty liver was determined at each examination by ultrasound. Cox proportional hazards models were used to evaluate the association of baseline and time-dependent levels of serum uric acid with incident fatty liver, adjusted for potential confounders. During 23 995 person-years of follow-up, 1717 participants developed fatty liver on ultrasound examination. After adjustment for age, body mass index, smoking, and alcohol intake, the hazard ratios (95% confidence intervals) for incident fatty liver comparing quartiles 2 to 4 of serum uric acid to quartile 1 were 1.17 (1.01-1.37), 1.28 (1.11-1.48), and 1.51 (1.31-1.73), respectively (P for trend = .001). The adjusted hazard ratio comparing participants with hyperuricemia (serum uric acid ≥7.0 mg/dL) to those with normouricemia (<7.0 mg/dL) was 1.29 (1.14-1.46). A graded and statistically significant association persisted after adjusting for other cardiometabolic factors and also in time-dependent models. Serum uric acid was an independent risk factor of incident fatty liver detected by ultrasonography. Additional research should clarify the mechanisms underlying this association and the role of hyperuricemia in the development of fatty liver.

1. Introduction

Nonalcoholic fatty liver disease comprises a spectrum of hepatic pathologies that resemble alcoholic liver disease in subjects without excessive alcohol consumption.[1] Nonalcoholic fatty liver disease is now considered a hepatic manifestation of insulin resistance and a feature of the metabolic syndrome [2,3]. Furthermore, nonalcoholic fatty liver disease is increasingly recognized as an independent cardiovascular risk factor [4,5].

Accumulating evidence indicates that uric acid is an independent risk factor for cardiovascular disease and metabolic abnormalities [6,7]. Increased uric acid levels have been associated with the presence of the metabolic syndrome [8,9], a condition linked to oxidative stress and insulin resistance [10]. Indeed, hyperuricemia often precedes the development of hyperinsulinemia [11,12], obesity[13], and diabetes [14,15]. In experimental and in in vitro models, uric acid may also induce inflammatory responses [16].

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Because uric acid levels may be related to oxidative stress, inflammation, and insulin resistance, all contributing mechanisms for nonalcoholic fatty liver disease [17,18], it has been hypothesized that uric acid can play a role in the development of nonalcoholic fatty liver disease [19,20]. A few cross-sectional or retrospective studies have shown an association between serum uric acid levels and prevalent nonalcoholic fatty liver disease [19-22], but no longitudinal study has evaluated the prospective association between serum uric acid and the development of nonalcoholic fatty liver disease.

In the present study, we examined if serum uric acid levels predict future nonalcoholic fatty liver disease as determined by ultrasonography, a practical and reliable method for detecting fatty liver [23,24]. Furthermore, we assessed if this association persisted when time-dependent changes in serum uric acid levels and in other potential confounders were taken into account.

2. Materials and methods

2.1. Subjects

The study population was composed of male workers from one of the largest semiconductor manufacturing companies in Korea and its 13 affiliates [25,26]. In Korea, the Industrial Safety and Health Law requires employees to participate in annual or biennial health examinations. The present cohort included all male workers 30 to 59 years of age from the above-mentioned semiconductor companies who participated in comprehensive health examinations at the Kangbuk Samsung Hospital in Seoul, Korea, in 2002 (N = 15 347). All these workers underwent ultrasound examination of the liver.

For this analysis, we excluded participants with evidence of liver disease or with major risk factors for liver disease at baseline. Thus, we excluded 5053 subjects with ultrasonographic evidence of fatty liver; 5013 subjects with elevated alanine aminotransferase (ALT) levels (≥35 U/L); 2867 subjects reporting an alcohol intake of at least 20 g/d [27]; 852 subjects with positive serologic markers for hepatitis B or C virus, with a reported history of known liver disease (including viral, genetic, autoimmune, and drug-induced liver disease), with abnormal liver ultrasound findings (indicating chronic liver disease, liver cirrhosis, intrahepatic or extrahepatic cholelithiasis, or abnormal dilatation of the biliary tree), or taking medications for hepatitis; 431 subjects who had taken medications within the past year that could affect the development of hepatic steatosis (such as steroids, immune suppressants, anticonvulsants, or tetracyclines); 27 subjects with a history of malignancy; 16 subjects with a history of cardiovascular disease; 125 subjects currently using lipid-lowering drugs; 279 subjects with diabetes; and 34 subjects taking medications for hyperuricemia or gout. We further excluded 337 subjects with missing baseline data on their medical histories and 638 subjects who did not attend any follow-up visit between 2002 and 2008. The final sample size was 5741 participants.

This study was approved by the Institutional Review Board of the Kangbuk Samsung Hospital. The informed consent requirement for this study was exempted by the Institutional Review Board because researchers only accessed retrospectively a deidentified database for analysis purposes.

2.2. Measurements

Baseline and follow-up examinations were conducted at the Kangbuk Samsung Hospital. Study participants were examined annually or biennially until December 2008. The average follow-up period for participants who did not develop ultrasonographically detected fatty liver was 4.9 years.

Health examinations collected data on sociodemographic characteristics, medical history, medication use, health-related behaviors, physical measurements, and serum biochemical measurements [26]. Questions pertaining to alcohol intake included weekly frequency of alcohol consumption and usual daily amount of consumption. Questionnaire data were also used to identify current smokers and to assess the weekly frequency of moderate- or vigorous-intensity physical activity. Body weight was measured with light clothing and without shoes to the nearest 0.1 kg using a digital scale. Height was measured to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Trained nurses measured sitting blood pressure with a standard mercury sphygmomanometer.

Blood specimens were sampled from the antecubital vein after more than 12 hours of fasting. Serum levels of glucose, uric acid, total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, γ-glutamyltransferase (GGT), ALT, aspartate aminotransferase, and alkaline phosphatase were measured using Bayer Reagent Packs on an automated chemistry analyzer (Advia 1650 Auto Analyzer; Bayer Diagnostics, Leverkusen, Germany). Measurement techniques included the hexokinase method for glucose, an enzymatic colorimetric assay for serum lipids, and an immunoradiometric assay for insulin (Biosource, Nivelles, Belgium). The serum uric acid method was based on the Fossati enzymatic reaction using uricase with a Trinder-like end point (ADVIA 1650 Auto Analyzer). Insulin resistance was assessed with the homeostasis model assessment of insulin resistance (HOMA-IR), according to the following equation: fasting blood insulin (in microunits per milliliter) × fasting blood glucose (in millimoles per liter)/22.5. High-sensitivity C-reactive protein (hsCRP) was analyzed by particle-enhanced immunonephelometry with the BNII System (Dade Behring, Marburg, Germany) using a lower detection limit of 0.175 mg/L. The clinical laboratory has been accredited and participates annually in inspections and

surveys by the Korean Association of Quality Assurance for Clinical Laboratories.

Abdominal ultrasounds were performed with a 3.5-MHz transducer (Logic Q700 MR; GE, Milwaukee, WI) by 12 experienced radiologists who were unaware of the aims of the study and blinded to laboratory values. Images were captured in a standard fashion with the patient in the supine position with the right arm raised above the head [25]. An *ultrasonographic diagnosis of fatty liver* (USFL) was defined as the presence of a diffuse increase of fine echoes in the liver parenchyma compared with the kidney or spleen parenchyma [28]. Ultrasonographic diagnosis of fatty liver was determined by the radiologists using live images.

Metabolic syndrome was defined as the presence of 3 or more Adult Treatment Panel III criteria [29]: (1) abdominal obesity, (2) fasting blood glucose of at least 110 mg/dL, (3) triglycerides of at least 150 mg/dL, (4) HDL cholesterol less than 40 mg/dL, and (5) blood pressure of at least 130/85 mm Hg. Because waist circumference measurements were not available for all subjects, we substituted overall adiposity (ie, a BMI $\geq$25 kg/m^2, which has been proposed as a cutoff for the diagnosis of obesity in Asians [30]) for abdominal obesity. *Diabetes* was defined as a fasting serum glucose of at least 126 mg/dL or current use of blood glucose–lowering agents.

2.3. Statistical analysis

One-way analysis of variance and χ^2 tests were used to compare the characteristics of study participants at baseline by quartiles of serum uric acid (<5.2, 5.2-5.7, 5.8-6.4, and $\geq$ 6.5 mg/dL). For incident USFL cases, the time of USFL occurrence was assumed to be the midpoint between the visit at which USFL was first diagnosed and the previous visit. Person-years were calculated as the sum of the follow-up duration from baseline until occurrence of USFL or until the final examination of each individual, whichever came first.

We used Cox proportional hazards models to estimate adjusted hazard ratios (and 95% confidence intervals [CIs]) for incident USFL comparing the highest 3 quartiles of baseline serum uric acid to the lowest quartile. The decisions on adjustment variables were made a priori based on biological and clinical considerations. After initial age-adjusted models, we adjusted for potential confounders (BMI, smoking, alcohol intake, and exercise) and then for other metabolic markers (ALT, fasting blood glucose, systolic blood pressure, total cholesterol, triglycerides, HDL cholesterol, HOMA-IR, CRP, and the presence of metabolic syndrome) to evaluate if the association of uric acid with incident USFL was independent of other metabolic abnormalities. For testing linear risk trends, we used the quartile rank as a continuous variable in the regression models. We checked the proportional hazards assumption by examining graphs of estimated log(−log) survival.

In addition, we compared the risk of USFL in hyperuricemic participants (serum uric acid $\geq$7.0 mg/dL [416.4 μmol/L]) vs normouricemic participants; and we estimated the hazard ratio for incident USFL associated with an increase of 1 mg/dL in serum uric acid modeled as a

Table 1
Baseline characteristics of study participants by quartile of serum uric acid

	Uric acid					*P* trend
	Overall (n = 5741)	Quartile 1 (n = 1382)	Quartile 2 (n = 1337)	Quartile 3 (n = 1502)	Quartile 4 (n = 1520)	
Uric acid (range, mg/dL)	0.8-11.5	0.8-5.1	5.2-5.7	5.8-6.4	6.5-11.5	
Age (y)	36.7 (4.9)	37.4 (5.2)	36.6 (4.8)	36.5 (4.7)	36.5 (4.7)	<.001
BMI (kg/m^2)	22.9 (2.4)	22.3 (2.4)	22.6 (2.4)	22.9 (2.3)	23.5 (2.3)	<.001
Current smoker (%)	43.5	45.3	43.3	43.6	41.9	.09
Alcohol intake (% drinking 10-20 g/d)	27.6	24.5	26.0	27.2	32.2	<.001
Regular exercise (%)[a]	51.3	51.3	49.0	51.8	52.8	.22
Metabolic syndrome (%)	4.5	3.0	3.7	4.5	6.6	<.001
Hypertension (%)	11.6	9.5	10.7	11.6	14.4	<.001
Systolic BP (mm Hg)	114.0 (12.1)	112.9 (11.9)	113.8 (11.7)	113.6 (12.0)	115.5 (12.4)	<.001
Diastolic BP (mm Hg)	73.7 (9.6)	72.8 (9.4)	73.7 (9.1)	73.5 (9.6)	74.9 (10.0)	<.001
Glucose (mg/dL)	89.6 (8.8)	89.1 (9.2)	88.9 (8.7)	89.9 (8.6)	90.5 (8.7)	<.001
Total cholesterol (mg/dL)	194.5 (32.1)	189.6 (31.8)	191.9 (29.8)	195.7 (32.4)	200.1 (33.1)	<.001
HDL cholesterol (mg/dL)	53.5 (11.5)	54.7 (12.1)	53.8 (11.4)	53.4 (11.6)	52.3 (10.9)	<.001
LDL cholesterol (mg/dL)	116.1 (27.6)	112.4 (27.2)	114.5 (26.1)	117.1 (28.0)	119.8 (28.2)	<.001
Triglycerides (mg/dL)	109 (82-149)	100 (75-136)	104 (80-142)	109 (84-145)	124 (90-169)	<.001
ALT (U/L)	20 (16-25)	19 (16-24)	20 (16-24)	20 (16-25)	21 (17-27)	<.001
AST (U/L)	21 (19-24)	21 (18-24)	21 (19-24)	21 (19-24)	22 (19-25)	<.001
GGT (U/L)	20 (15-27)	18 (14-24)	19 (15-25)	20 (15-27)	22 (17-31)	<.001
hsCRP (mg/L)	0.4 (0.02-0.8)	0.3 (0.2-0.7)	0.3 (0.2-0.7)	0.4 (0.2-0.8)	0.5 (0.2-1.0)	<.001
Insulin (μU/dL)	6.30 (5.07-8.17)	5.95 (4.87-7.61)	6.23 (5.05-7.97)	6.39 (5.14-8.29)	6.60 (5.21-8.80)	<.001
HOMA-IR	1.37 (1.09-1.82)	1.29 (1.05-1.67)	1.34 (1.09-1.79)	1.41 (1.10-1.85)	1.46 (1.13-1.95)	<.001

Data are means (standard deviation), medians (interquartile range), or percentages. BP indicates blood pressure; AST, aspartate aminotransferase.

[a] At least once a week.

Table 2
Hazard ratios (95% CIs) for incident ultrasonographically detected fatty liver by serum uric acid quartiles

	Uric acid				*P* trend
	Quartile 1 (n = 1382)	Quartile 2 (n = 1337)	Quartile 3 (n = 1502)	Quartile 4 (n = 1520)	
No. of incident cases	320	368	452	577	
Incidence rate (/100 person-y)	5.3	6.4	7.2	9.6	
Model 1	1.00 (reference)	1.21 (1.04-1.40)	1.37 (1.19-1.58)	1.84 (1.60-2.11)	<.001
Model 2	1.00 (reference)	1.17 (1.01-1.37)	1.28 (1.11-1.48)	1.51 (1.31-1.73)	.001
Model 3	1.00 (reference)	1.11 (0.95-1.30)	1.14 (0.98-1.32)	1.34 (1.15-1.55)	.001
Time-dependent model	1.00 (reference)	0.94 (0.77-1.15)	1.12 (0.93-1.35)	1.31 (1.10-1.56)	<.001

Model 1: age adjusted. Model 2: further adjusted for age, BMI, smoking, alcohol intake, and exercise. Model 3 and time-dependent model: further adjusted for total cholesterol, HDL cholesterol, triglycerides, glucose, systolic blood pressure, insulin, hsCRP, and the presence of metabolic syndrome.

continuous variable. Finally, we used repeated measurements of serum uric acid and of other covariates in time-dependent Cox proportional hazards models during follow-up. Statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC) and Stata version 11 (StataCorp, College Station, TX). All reported *P* values were 2-tailed, and statistical significance was set at $P < .05$.

3. Results

At baseline, the mean (SD) age, BMI, and serum uric acid levels of study participants were 36.7 (4.9) years, 22.9 (2.4) kg/m^2, and 5.8 (1.1) mg/dL, respectively (Table 1). The prevalences of current smoking, hypertension, and metabolic syndrome were 43.5%, 11.6%, and 4.5%, respectively. Serum uric acid levels were positively associated with a variety of metabolic parameters, including BMI, systolic and diastolic blood pressure, glucose, total cholesterol, LDL cholesterol, triglycerides, liver enzymes, hsCRP, insulin, and HOMA-IR (Table 1). Serum uric acid levels were also positively associated with alcohol intake and with the prevalence of hypertension and the metabolic syndrome. Age and HDL cholesterol were inversely associated with serum uric acid levels.

During 23 995 person-years of follow-up, 1717 participants developed USFL (rate, 7.2/100 person-years). Increasing levels of serum uric acid were progressively associated with increasing incidence of USFL (Table 2). In age-adjusted models, the hazard ratios for USFL comparing quartiles 2 to 4 vs quartile 1 of serum uric acid were 1.21 (95% CI, 1.04-1.40), 1.37 (1.31-1.73), and 1.84 (1.60-2.11), respectively. After adjusting for BMI, smoking, alcohol intake, and exercise, the hazard ratio for USFL in the highest quartile compared with the lowest was 1.51 (1.31-1.73, *P* trend = .001). The association also persisted after adjusting for multiple metabolic parameters (hazard ratio comparing the highest to the lowest quartile, 1.34; 95% CI, 1.15-1.55; *P* trend = .001) and after introducing serum uric acid and metabolic risk factors as time-dependent exposures (hazard ratio comparing the highest to the lowest quartile, 1.31; 95% CI, 1.10-1.56; *P* trend < .001). Further adjustment for estimated glomerular filtration rate did not materially alter the estimates (not shown).

The multivariate-adjusted hazard ratio comparing hyperuricemic (≥7.0 mg/dL) vs normouricemic (<7.0 mg/dL) participants was 1.21 (95% CI, 1.07-1.38; *P* = .004) (Table 3). Finally, when serum uric acid was introduced as a continuous variable in multivariate models, the hazard ratio for USFL associated with an increase of 1 mg/dL in uric acid was 1.11 (95% CI, 1.06-1.16; $P < .001$).

The association between the presence of hyperuricemia and the incidence of USFL was also examined by subgroups of study participants (Fig. 1). Hyperuricemia was significantly more strongly associated with incident USFL in nonobese compared with obese participants (adjusted hazard ratios, 1.44 vs 1.03, respectively; *P* interaction = .02) and in participants with normal triglyceride levels compared with

Table 3
Hazard ratios (95% CIs) for incident ultrasonographically detected fatty liver for clinically elevated serum uric acid

	Hyperuricemia (≥7.0 mg/dL)				*P* value
	No (n = 4971)	Yes (n = 770)	*P* value (n = 1502)	Per 1-mg/dL increase in uric acid (n = 5741)	
No. of incident cases	1412	305		1717	
Incidence rate (/100 person-y)	6.7	10.3		7.2	
Model 1	1.00 (reference)	1.54 (1.36-1.75)	<.001	1.23 (1.18-1.29)	<.001
Model 2	1.00 (reference)	1.29 (1.14-1.46)	<.001	1.15 (1.10-1.20)	<.001
Model 3	1.00 (reference)	1.21 (1.07-1.38)	.004	1.11 (1.06-1.16)	<.001
Time-dependent model	1.00 (reference)	1.20 (1.02-1.40)	.025	1.11 (1.05-1.18)	<.001

Model 1: age adjusted. Model 2: further adjusted for age, BMI, smoking, alcohol intake, and exercise. Model 3 and time-dependent model: further adjusted for total cholesterol, HDL cholesterol, triglycerides, glucose, systolic blood pressure, insulin, hsCRP, and the presence of metabolic syndrome.

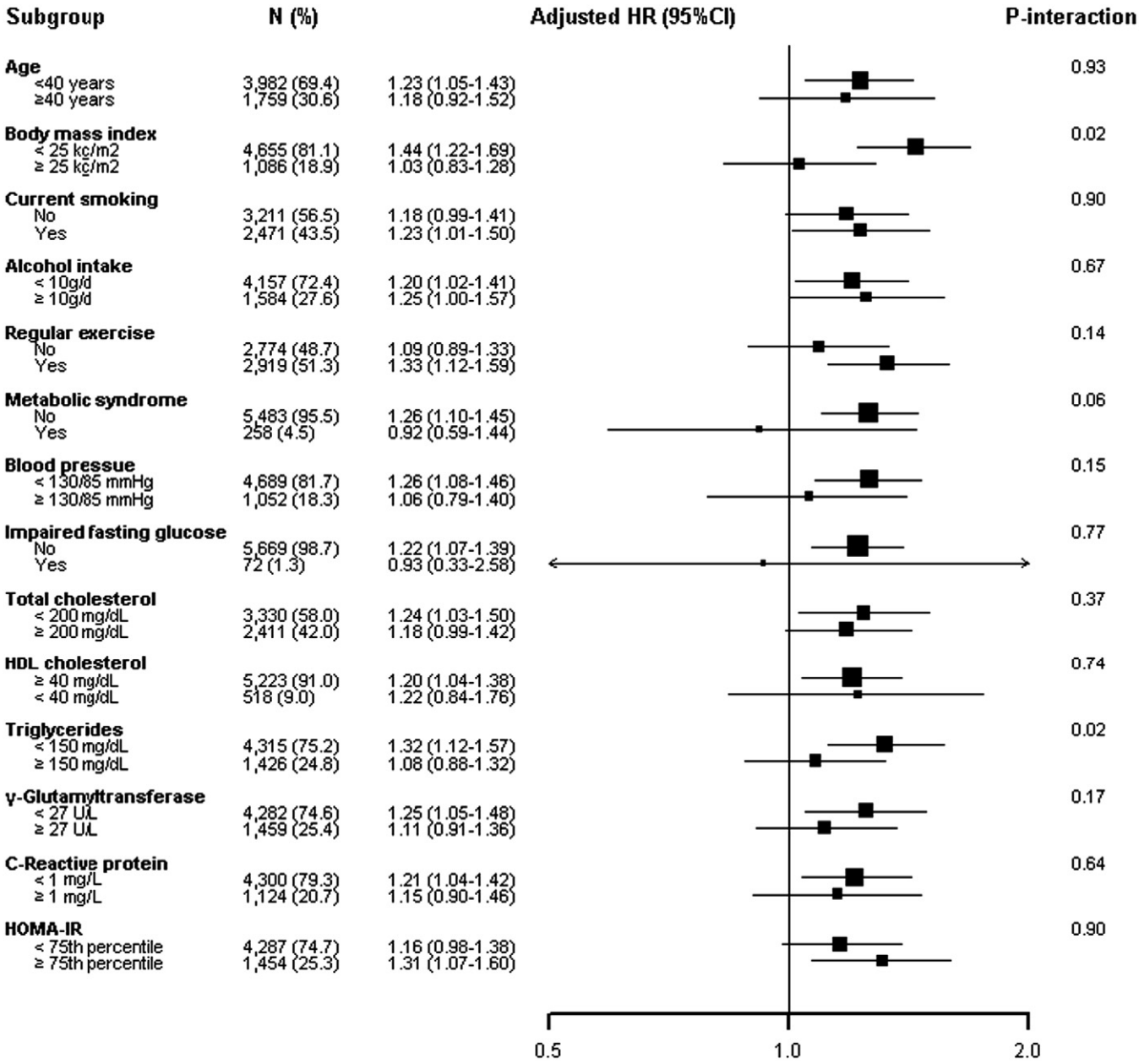

Fig. 1. Adjusted hazard ratio for ultrasonographically detected fatty liver comparing hyperuricemic (≥7.0 mg/dL) vs normouricemic (<7.0 mg/dL) participants in clinically relevant subgroups. Adjusted for other covariates in the figure. The 75th percentile for HOMA-IR was 1.82.

those with high triglyceride levels (adjusted hazard ratios, 1.32 vs 1.08, respectively; *P* interaction = .02).

4. Discussion

In this longitudinal study of healthy Korean men apparently free of liver disease at baseline, increased levels of serum uric acid predicted the development of USFL even after adjusting for BMI and for a variety of cardiometabolic parameters. Indeed, the association between uric acid and incident USFL was significantly stronger among nonobese participants and in participants with normal triglycerides. Our study extends the findings of previous cross-sectional studies [19-22] and indicated that elevated serum uric acid is a prospective predictor of USFL in a healthy population.

A variety of mechanisms may explain the prospective association of serum uric acid levels with fatty liver disease, including hyperuricemia-induced endothelial dysfunction [7,31] and inflammatory and oxidative damage [16]. Finally, uric acid levels have also been associated with the development of cirrhosis and with the presence of elevated serum liver enzymes after adjustments for other important causes and risk factors of chronic liver disease [32].

Although there has been controversy in the literature over the role of uric acid in cardiometabolic disorders,

accumulating evidence indicates that uric acid is an independent cardiovascular risk factor [7]. Elevated uric acid levels often precede the development of hyperinsulinemia [11], obesity [13], diabetes [7,14], and hypertension [7]. Uric acid levels can also predict early stages of renal disease [33,34], and a recent small clinical trial reported cardiovascular and renal benefits of lowering uric acid levels [35].

In contrast to previous studies that could not determine a clear temporal relationship, the prospective design of our study allowed us to establish a clear temporal relationship between serum uric acid levels and incident USFL, even after adjusting for multiple cardiometabolic parameters and estimated glomerular filtration rate. Our study population was younger and leaner than those in other studies, and we systematically excluded medical conditions or medications that could be related to liver disease.

Some strengths of our study include the large sample size and the prospective design that allows for estimation of incidence of new cases of fatty liver. Some limitations, however, also need to be considered in the interpretation of our findings. First, our study used USFL as the study end point and lacked histologic confirmation for fatty liver [23,24], although studies using ultrasound and biopsy support that ultrasonographic results reliably predict fatty liver. Second, we did not have information on the intra- or interobserver variability of liver ultrasound examinations. However, all examinations were interpreted by experienced radiologists evaluating live echo images using widely established methods and criteria. Any errors in the interpretation of abdominal ultrasounds are independent of serum uric acid determinations and thus will tend to suppress effect estimates and *P* values toward the null but would not affect the importance of the significant results presented herein. Third, we used a modified National Cholesterol Education Program definition of metabolic syndrome based on BMI instead of waist circumference. A number of studies have also shown that BMI can be as effective as waist circumference for predicting the development of type 2 diabetes mellitus and other metabolic disturbances [36,37]. Fourth, alcohol intake, based on self-report, may have been underestimated [38]. Nevertheless, the relationship between hyperuricemia and incident USFL remained similar and significant even after exclusion of participants with serum GGT levels greater than the 75th percentile in our study population [26].

Serum uric acid appears to be an independent predictor for developing ultrasonographically detected fatty liver even in normal-weight men. The association of uric acid with fatty liver and other metabolic abnormalities may be particularly important in the early phases of the disease and may provide additional hints to detect or intervene on subjects at risk of future disease. Additional research should clarify the mechanisms underlying this association and the interplay of hyperuricemia and other metabolic abnormalities in the development of fatty liver.

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