Clinical Chemistry 54:2
310–316 (2008)

Plasma Uric Acid and the Risk of Type 2 Diabetes in a Chinese Community

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BACKGROUND: Previous cross-sectional studies have shown hyperuricemia to be prevalent among individuals with metabolic syndrome, but the evidence from prospective studies of an association between uric acid and diabetes risk is limited. We prospectively investigated the association between plasma concentrations of uric acid and the incidence of type 2 diabetes in Chinese individuals.

METHODS: We conducted a community-based prospective cohort study of 2690 participants (age range, 35–97 years) in the Chin-Shan Community Cardiovascular Cohort Study, who were found to be free of diabetes and cardiovascular disease during baseline assessment at study entry in 1990. During a median 9.0-year follow-up, 548 participants developed type 2 diabetes.

RESULTS: High plasma uric acid concentrations were associated with a higher prevalence of metabolic syndrome. After adjustment for age, sex, body mass index, and other covariates, the relative risks (RR) of diabetes according to uric acid quintile were 1.11, 1.29, 1.40, and 1.63 [95% confidence interval (CI), 1.20–2.23; P for trend <0.001]. After additional adjustment for metabolic syndrome, the RR for comparing the participants in the fifth and first uric acid quintiles was 1.40 (95% CI, 1.02–1.92; P for trend = 0.027). In joint analyses, participants who were in the highest uric acid quintile and also had metabolic syndrome had a 3.3-fold greater risk of diabetes (95% CI, 2.27–4.94) than those in the lowest uric acid quintile and without metabolic syndrome.

CONCLUSIONS: These findings suggest a modest positive association between plasma uric acid concentration and the incidence of type 2 diabetes in Chinese individuals. The association between hyperuricemia and diabetes was partly mediated through the metabolic syndrome.

Identifying the risk factors for the development of type 2 diabetes is essential for primary prevention *(1)*. Metabolic syndrome and insulin resistance are well-established key risk factors for diabetes. Hyperuricemia, a highly prevalent condition in the adult population, is associated with obesity and insulin resistance *(2)*. Although much of the literature addresses the association of hyperuricemia, hypertension, and renal disease *(3, 4)*, the role of uric acid in diabetes risk remains controversial. Recent evidence suggests that uric acid plays a role in immune activation *(5)* and cytokine secretion *(6)*. Moreover, uric acid has been identified as a mediator of endothelial dysfunction and systemic inflammation *(7)*. Previous cross-sectional data showed that hyperuricemia to be prevalent among individuals with metabolic syndrome *(8)*, but the evidence from prospective studies of an association between uric acid and diabetes risk is limited. Therefore, we conducted a prospective community-based cohort study to examine the association between plasma uric acid concentration and the risk of type 2 diabetes among ethnic Chinese in Taiwan.

Materials and Methods

STUDY DESIGN AND STUDY PARTICIPANTS

Details of this cohort study have been published *(9–11)*. In brief, the Chin-Shan Community Cardiovascular Cohort Study began in 1990 by recruiting 1703 men and 1899 women of Chinese ethnicity age 35 years and older from the Chin-Shan township, 30 km north of metropolitan Taipei, Taiwan. Information about anthropometry, lifestyle, and medical conditions was as-

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Received July 20, 2007; accepted November 15, 2007.
Previously published online at DOI: 10.1373/clinchem.2007.095190

sessed by interview questionnaires in 2-year cycles for the initial 6 years, and the validity and reproducibility of the collected data have been reported in detail *(12)*.

In brief, all study participants were individually interviewed with a structured questionnaire in the baseline survey (1990). Trained medical students canvassed door to door with the assistance of community leaders to extend invitations to participate in the baseline survey to collect information about sociodemographic characteristics, lifestyle behaviors, regular exercise, and personal and family histories of diseases and hospitalizations. With the consent of participants, physicians and students conducted physical examinations and laboratory tests for those participants invited to the clinic. Body mass index (BMI)[5] was calculated as the weight in kilograms divided by the height in meters squared. Waist circumference was measured with a measuring tape positioned midway between the lowest rib and the iliac crest. The measurement was made at minimal respiration status, with the tape snug but without compressing the skin. In 1990, we measured plasma biochemical biomarkers, including lipids, uric acid, and glucose, and assessed renal function; we repeated these measurements in the subsequent follow-up cycles until 2000.

Participants with incomplete blood data (n = 41), a diagnosis of diabetes (fasting glucose ≥7.0 mmol/L or with a history of hypoglycemic medication, n = 473), or a cardiovascular disease and cancer history (n = 170) at baseline were excluded from this investigation. After these exclusions, the final analytic sample included 2960 participants. During the follow-up from 1990–2000 (median, 8.97 years; interquartile range, 4.25–9.26 years), 548 individuals developed type 2 diabetes, which was defined as a fasting glucose concentration ≥7.0 mmol/L or by the use of oral hypoglycemic medications or insulin. The National Taiwan University Hospital Committee Review Board approved the study protocol.

MEASUREMENT OF BIOCHEMICAL MARKERS

The procedure for blood collection has been reported elsewhere *(13, 14)*. In brief, all venous blood samples drawn after a 12-h overnight fast were immediately refrigerated and transported within 6 h to the National Taiwan University Hospital. Serum samples were then stored at −70 °C before batch assay of total cholesterol, triglycerides, and HDL cholesterol. Standard enzymatic tests for serum cholesterol and triglycerides were used (Merck 14354 and 14366, respectively). HDL cholesterol was measured in supernatants after the precipitation of specimens with magnesium chloride/phosphotungstate reagents (Merck 14993). LDL cholesterol concentrations were calculated as the total cholesterol concentration minus the cholesterol concentration in the supernatant, as measured by the precipitation method (Merck 14992) *(15)*. The plasma uric acid concentration was assayed in an Eppendorf 5060 autoanalyzer (Eppendorf) by means of a commercial method (Merck) based on the uricase and peroxidase principle *(16)*.

A standard 75-g oral glucose-tolerance test was performed, and fasting and 2-h plasma glucose and insulin concentrations were measured in 1994 and 1995 *(13)*. Blood samples for glucose analysis were drawn into glass test tubes, each of which contained 80 mmol/L fluoride/oxalate. After centrifugation at 1500*g* at 4 °C for 10 min, the concentration of glucose in the supernatant was measured with a glucose dehydrogenase enzymatic assay (Merck 3389 method) in an Eppendorf 5060 autoanalyzer, and the plasma concentration of insulin was measured by an ELISA method with reagents supplied by Dako *(17)*. The homeostasis model assessment (HOMA) insulin-resistance index was calculated as: [(fasting plasma glucose in mmol/L) × (fasting insulin in mU/L)]/22.5 *(18)*. These data were available from the active participants in 1994 (n = 1 798). We followed the criteria of the Adult Treatment Panel III guideline to define metabolic syndrome *(19)* and used an Asian-specific waist-circumference cutoff point *(20)*.

STATISTICAL ANALYSIS

We classified participants on the basis of quintiles of serum uric acid concentrations, and continuous variables were presented as the mean (SD) or as the median. Relationships between the baseline uric acid concentration and other biomarkers were examined by evaluating age- and sex-adjusted Spearman partial correlation coefficients.

The incidence rates of diabetes were calculated by dividing the number of cases by the number of person-years of follow-up for each uric acid quintile. The relative risk (RR) of diabetes was calculated by dividing the incidence rate for each quintile by the rate in the first quintile. We used Cox proportional hazards models to adjust for potential confounding variables, including age group (35–44 years, 45–54 years, 55–64 years, 65–74 years, or ≥75 years), sex, BMI (<18 kg/m^2, 18–20.9 kg/m^2, 21–22.9 kg/m^2, 23–24.9 kg/m^2, or ≥25 kg/m^2), alcohol intake (nondrinker/current), smoking (yes/no), regular exercise (yes/no), marital status (single, married, or divorced), educational level (<9 years/≥9 years), occupation (no work, manual work, or professional), and family history of diabetes (yes/no). We further adjusted for metabolic syndrome to examine whether the association between uric acid

[5] Nonstandard abbreviations: BMI, body mass index; RR, relative risk; HOMA, homeostasis model assessment; CI, confidence interval.

Table 1. Characteristics of the population at baseline (1990) according to uric acid quintile for the 2960 participants.

	Quintile of baseline uric acid concentration					
	1 (n = 608)	2 (n = 596)	3 (n = 591)	4 (n = 584)	5 (n = 579)	*P*
Sex, %						<0.0001
Men	15.3	30.0	47.7	65.9	78.2	
Current smoker (yes), %	13.8	24.5	37.6	48.0	57.0	<0.0001
Alcohol drinking (yes), %	13.3	18.1	28.4	40.6	48.9	<0.0001
Marital status, %						0.22
Single	2.3	3.0	3.2	1.7	3.5	
Lived with spouse	85.7	86.7	85.2	88.2	88.6	
Divorced or separated	12.0	10.2	11.6	10.1	7.9	
Education level, %						0.001
<9 years	95.4	95.5	94.8	94.0	90.2	
≥9 years	4.6	4.5	5.3	6.0	9.8	
Job status, %						<0.0001
No job	57.1	54.0	50.4	42.5	35.2	
Farmer, laborer	29.1	32.1	33.7	40.8	44.2	
Professional, business	13.8	13.9	15.9	16.8	20.6	
Regular exercise (yes), %	13.2	13.4	12.9	15.1	18.0	0.08
Family history of diabetes, %	7.2	7.6	8.5	11.3	8.8	0.10
Metabolic syndrome, %	11.2	15.1	15.9	22.9	26.3	<0.0001
Age, years[a]	51.9	53.0	54.6	55.7	54.8	<0.0001
BMI, kg/m^2[a]	22.6	22.9	23.1	23.7	24.2	<0.0001
Uric acid, mmol/L[a]	0.211	0.278	0.324	0.377	0.486	<0.0001
HOMA-IR[a,b]	1.48	1.63	1.77	1.93	2.16	0.0002
CRP, mg/L[b]	1.0 (0.6–2.1)	1.1 (0.6–2.9)	1.0 (0.6–2.3)	1.2 (0.7–2.1)	1.5 (0.9–3.2)	0.0002

[a] Data are expressed as the mean.
[b] HOMA-IR, HOMA insulin resistance. Measurements were available for a subsample (n = 1 798).
[c] CRP, C-reactive protein. Data are expressed as the median (interquartile range). Measurements were available only for a subsample (n = 790).

concentration and diabetes was mediated through the metabolic syndrome. To test for a linear trend across uric acid quintiles, we used the median uric acid concentration for each category as a continuous variable in the multivariate model. We also used the test of Hosmer and Lemeshow to evaluate the goodness of fit for the model *(21)*.

All statistical tests were 2-tailed with a type I error of 0.05, and *P* values <0.05 were considered statistically significant. Analyses were performed with SAS software (version 9.1; SAS Institute) and Stata (version 9.1; Stata Corporation).

Results

Participants in the highest uric acid quintile were older and more likely to be male and have a higher BMI value than the participants in the other quintiles. They were also more likely to smoke and drink alcohol and had a higher prevalence of metabolic syndrome (Table 1).

Uric acid concentration was inversely correlated with HDL and positively correlated with BMI, waist circumference, triglycerides, and insulin resistance (Table 2). Uric acid concentrations adjusted for age, sex, and BMI increased substantially with the number of metabolic syndrome components (*P* for trend <0.0001) (Fig. 1).

We documented 548 incident cases of diabetes during a median follow-up of 9.0 years. Table 3 shows the RRs and 95% confidence intervals (CIs) for diabetes according to uric acid quintile at baseline. After adjustment for age, sex, BMI, and other covariates, the RRs of diabetes according to uric acid quintile were 1.11, 1.29, 1.40, and 1.63 (95% CI, 1.20–2.23;

Table 2. Age- and sex-adjusted Spearman correlation coefficients between variables measured in the study participants.

	BMI	Waist	Systolic BP[a]	Diastolic BP	Total cholesterol	Triglycerides	HDL	LDL	Fasting glucose	HOMA
Uric acid	0.29	0.29	0.16	0.18	0.17	0.29	−0.17	0.21	0.09	0.24
BMI		0.69	0.29	0.29	0.16	0.34	−0.33	0.24	0.18	0.44
Waist			0.26	0.24	0.14	0.32	−0.31	0.22	0.17	0.46
Systolic BP				0.72	0.09	0.23	−0.14	0.11	0.10	0.18
Diastolic BP					0.10	0.21	−0.12	0.13	0.12	0.20
Total cholesterol						0.27	0.11	0.94	0.11	0.11
Triglycerides							−0.44	0.38	0.18	0.29
HDL								−0.15	−0.15	−0.30
LDL									0.15	0.20
Fasting glucose										0.17

[a] BP, blood pressure.

P for trend <0.001). After additional adjustment for the metabolic syndrome, the RR for the comparison of the participants in the fifth and first uric acid quintiles was 1.40 (95% CI, 1.02–1.92; *P* for trend = 0.027).

In joint analyses of metabolic syndrome and uric acid concentration, participants with metabolic syndrome had a consistently higher risk than those without metabolic syndrome, independently of uric acid concentration (Fig. 2). The association between uric acid concentration and diabetes appears to be stronger among those with metabolic syndrome than those without it, although the *P* value for interaction was not statistically significant (*P* for interaction = 0.57). Participants who were in the highest uric acid quintile and also had metabolic syndrome had a 3.3-fold greater risk of diabetes (95% CI, 2.27–4.94) than those in the lowest uric acid quintile and without metabolic syndrome.

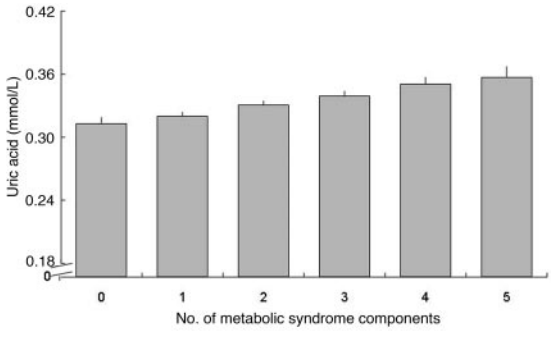

Fig. 1. Adjusted mean uric acid concentrations in the study participants according to the number of metabolic syndrome components.

Data are expressed as the mean (SD) and adjusted for age, sex, and BMI (*P* for trend <0.0001).

In additional analyses, we included quintiles of the HOMA insulin-resistance index in the multivariate model for the available samples (n = 1798). The association between uric acid concentration and diabetes was further attenuated and became nonsignificant (RR for comparison of the extreme quintiles, 1.22; 95% CI, 0.85–1.74; *P* for trend = 0.28).

Discussion

Our data suggest a positive association between the plasma concentration of uric acid and the incidence of type 2 diabetes in Chinese individuals. This association was somewhat attenuated after adjustment for metabolic syndrome, suggesting that the association between hyperuricemia and diabetes was partly mediated through the metabolic syndrome. In our study, the uric acid concentration increased monotonically with the number of metabolic syndrome components.

Cross-sectional studies have suggested a positive association between uric acid and diabetes in several populations, including Italian adults *(22)*, Asians *(23–25)*, and inhabitants of Seychelles *(26)*. A cross-sectional study of 1877 Turkish men and women showed that those in the highest uric acid tertile had an odds ratio of 1.89 (95% CI, 1.45–2.46) for a diagnosis of diabetes, compared with the lowest tertile *(27)*. Furthermore, in a cross-sectional study of 8144 Japanese men and women, the odds ratios for diabetes for comparisons of the highest and lowest uric acid quartiles were 4.17 (95% CI, 2.56–6.79) for women and 1.97 (95% CI, 1.61–2.40) for men.

Table 3. Median uric acid concentrations, numbers of study participants, incident cases, person-years, rates, and RRs by uric acid quintile for the association with type 2 diabetes in the study participants, 1990–2000.

	Uric acid quintile					
	1	2	3	4	5	*P*, trend
Median uric acid, mmol/L	0.22	0.28	0.32	0.38	0.46	
Participants, n	608	596	591	584	579	
Incident cases, n	81	94	107	129	136	
Person-years, n	4494.0	4394.7	4137.8	4003.4	3750.1	
Rate/1 000	18.0	21.4	25.9	32.2	36.3	
RR, model 1[a,b]	1	1.19 (0.89–1.61)	1.49 (1.11–2.00)	1.84 (1.37–2.47)	2.12 (1.57–2.87)	<0.0001
RR, model 2[a,c]	1	1.11 (0.82–1.49)	1.29 (0.96–1.73)	1.40 (1.04–1.90)	1.63 (1.20–2.23)	0.0008
RR, model 3[a,d]	1	1.08 (0.80–1.46)	1.21 (0.90–1.63)	1.25 (0.92–1.70)	1.40 (1.02–1.92)	0.027

[a] Data for RR (95% CI) are expressed relative to uric acid quintile 1.
[b] Model 1: Adjusted for age groups (35–44, 45–54, 55–64, 65–74, and ≥75 years) and sex.
[c] Model 2: Model 1 plus BMI (<18, 18–20.9, 21–22.9, 23–24.9, or ≥25 kg/m^2), alcohol intake (nondrinker/regular), exercise (yes/no), marital status (single, married, or divorced/separated), education level (<9 years/≥9 years), occupation (no work, manual work, or professional), and family history of diabetes (yes/no).
[d] Model 3: Model 2 plus metabolic syndrome (yes/no).

Prospective cohort studies of uric acid and incident diabetes are limited and have yielded inconsistent findings. In a follow-up study of 6365 Japanese male employees ages 35–61 years from 1981–1997, uric acid concentration was associated with a small but nonsignificant increased risk of diabetes: The multivariate RR was 1.21 (95% CI, 0.88–1.65; *P* for trend = 0.77) for a comparison of participants in the fifth and first quintiles *(28)*. On the contrary, in a 6-year follow-up study of 2310 Japanese male adults, Nakanishi et al. demonstrated that uric acid concentration was significantly associated with an increased risk of an impaired result in the fasting glucose test and diabetes: The multivariate risk was 1.78 (95% CI, 1.11–2.85; *P* for trend = 0.03) in a comparison of participants in the highest and lowest quintiles *(29)*. The diagnosis of diabetes was different in these 2 Japanese studies. The study of Taniguchi et al. *(28)* included a diabetes outcome only for a

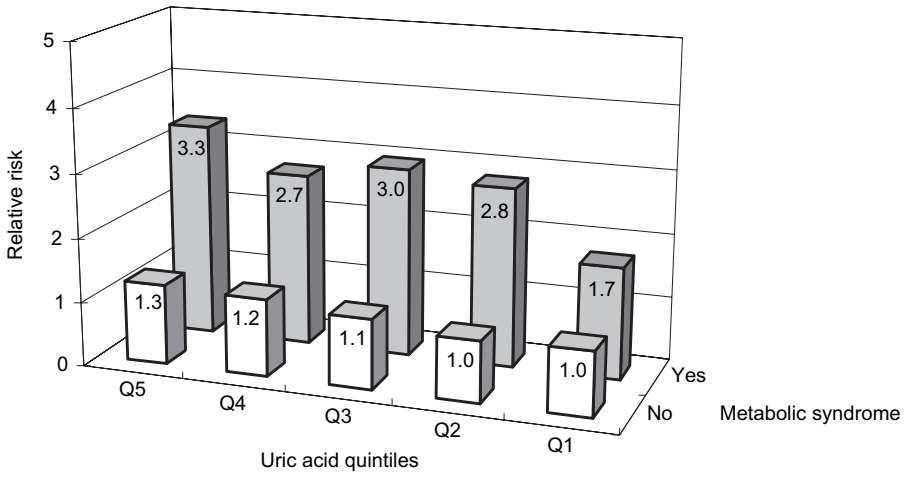

Fig. 2. RRs of diabetes during 9 years of follow-up according to uric acid quintile and the presence or absence of metabolic syndrome.

Adjusted for age, sex, BMI, alcohol intake, smoking, exercise habit, marital status, education, job status, and family history of diabetes.

fasting-glucose value ≥7.0 mmol/L or a glucose concentration after 2 h of ≥11.1 mmol/L. They did not include participants with a history of oral hypoglycemic medications or insulin use, and the incidence rates of diabetes were relatively low, only 6–8 cases per 1000 person-years. In contrast, the study of Nakanishi et al. *(29)* combined an impaired fasting-glucose status and diabetes as the outcome, an action that may have weakened the association with diabetes.

The positive association between uric acid concentration and diabetes may be explained by at least 3 potential mechanisms. First, metabolic syndrome, as a precursor of diabetes, induces high oxidative stress, which is worsened by the accompanying hyperuricemia *(30)*. Uric acid usually has an antioxidative effect; however, uric acid becomes a strong oxidant in the environment of metabolic syndrome *(31)*. This phenomenon of the urate redox shuttle may explain the paradoxical effects of uric acid on oxidative stress *(32)*. Inflammation and oxidative stress induced by metabolic syndrome and hyperuricemia may predispose individuals to a higher risk for diabetes.

Second, uric acid stimulates vascular smooth muscle proliferation and induces endothelial dysfunction *(33)*. Uric acid has been shown to decrease endothelial nitric oxide production and to lead to endothelial dysfunction and insulin resistance *(34, 35)*. Consequently, uric acid induces vascular inflammation and artery damage *(8, 33)*, which in turn leads to an increased risk of diabetes and atherosclerosis *(36, 37)*. A recent study showed that hyperuricemia was associated with the severity of carotid plaque among Japanese men *(38)*. The authors showed that metabolic syndrome explained most of the association between uric acid and carotid plaque, because adjusting for metabolic syndrome substantially attenuated the association *(38)*. In addition, our data show a positive association between uric acid concentration and the HOMA insulin-resistance index, and adjustment for the HOMA index further attenuated the association between uric acid concentration and diabetes. These data suggest that insulin resistance, which is closely related to metabolic syndrome and inflammation, may also mediate the association between uric acid and diabetes risk.

Third, uric acid is associated with increased renal glomerular pressure and increased renal sodium reabsorption, and these renal reactions are greatly enhanced by high insulin concentrations *(39)*. Among diabetic patients, hyperuricemia has been associated with microalbuminuria *(22)*. The combined effects of insulin resistance and hyperuricemia on renal functions may lead to increased glucose intolerance, hypertension, and diabetes risk.

To our knowledge, this study is the first prospective investigation of serum uric acid and the risk of diabetes among Chinese individuals. Because of the prospective cohort design, the baseline measurements of all cohort members were unlikely to have been affected by storage and laboratory issues that might be raised in some cross-sectional studies. The use of a community-based population may also have reduced the possibility of selection bias. We also included important socioeconomic and lifestyle factors in the models to control for potential confounding factors.

Our study had several potential limitations. First, this observational study did not clarify the time sequence of hyperuricemia and metabolic syndrome. A prospective study in Korea, however, suggested that a higher uric acid concentration predicted the incidence of hypertension and the development of metabolic syndrome *(25)*, and hyperuricemia has been considered to be a component of metabolic syndrome *(27, 31)*. Second, because baseline serum uric acid concentrations were measured only once, our results may be prone to intraindividual variations that might have attenuated our results. Finally, we were unable to obtain detailed information on antihypertensive medications and the intake of foods that might have affected plasma uric acid concentrations.

In conclusion, this prospective study suggests a positive association between the plasma concentration of uric acid and the incidence of type 2 diabetes in Chinese individuals. This association was somewhat attenuated after adjustment for metabolic syndrome, suggesting that the association between hyperuricemia and diabetes is partly mediated through the metabolic syndrome.

Grant/funding Support: This study was supported partly by grants from the National Science Council and Department of Health in Taiwan (NSC 96-2314-B-002-155, DOH 96D047). The research of F.B.H. is partly supported by an American Heart Association Established Investigator Award.

Financial Disclosures: None declared.

Acknowledgments: We thank the participants in the Chin-Shan community and the cardiologists at National Taiwan University Hospital for their assistance in this study.

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