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Predictors for Development of Hyperuricemia: An 8-Year Longitudinal Study in Middle-Aged Japanese Men

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To identify the factors responsible for increases in serum uric acid (SUA), a cohort of 1,312 hyperuricemia-free (SUA < 7.5 mg/dL and no medication for hyperuricemia or hypertension) male office workers aged 30 to 52 years were examined annually for 8 successive years. Subjects who were found to have become hyperuricemic (SUA ≥ 7.5 mg/dL) or who started medication for hyperuricemia during repeat surveys were defined as incidence cases. The SUA trend was also examined in 1,062 subjects for whom 9 consecutive SUA values were available and who did not start medication for hyperuricemia or hypertension during the observation period. Multivariate analyses, excluding the baseline SUA level as a factor in the Cox proportional-hazards model, indicated that age (negative), body mass index (BMI), log triglyceride level, hemoglobin A_{1c} (HbA_{1c}) level (negative), white blood cell count, and alcohol intake at study entry were significantly associated with the incidence of hyperuricemia. In the model including the baseline SUA level, baseline SUA level was the strongest factor for the incidence of hyperuricemia, and BMI, white blood cell count, and alcohol intake at study entry remained as independent factors. From stepwise linear regression analyses for SUA slope, excluding the baseline SUA level as a factor, significant correlates with SUA slope were, in order of their relative importance, slopes of BMI, HbA_{1c} (negative), blood urea nitrogen, log triglyceride level, total protein, and baseline levels of hematocrit (negative), white blood cells, and HbA_{1c} (negative). In stepwise linear regression analyses, including the baseline SUA level as a factor, SUA level (negative) and alcohol intake at study entry emerged as significant factors for SUA slope. The cumulative percentage of variation for SUA slope was 25.6%. In conclusion, obesity, alcohol intake, and multimetabolic disorders were determined to be independent predictors for the development of hyperuricemia. In addition, the white blood cell level may be a contributory factor.

JAPAN HAS RECENTLY experienced drastic changes in dietary habits with the rapid westernization of lifestyle, and intake of animal fat and protein and alcohol consumption have increased remarkably.[1] High serum uric acid (SUA) levels are causally associated with gout[2-4] and have been reported to be a risk factor for coronary heart disease.[2,3,5,6] Because recent changes in lifestyle in Japan therefore warrant concern, the factors related to hyperuricemia are of considerable interest.

Although secondary prevention with a focus on diagnosis and treatment of hyperuricemia is the goal of current medical efforts, long-term antihyperuricemic therapy involves both high costs and risks.[4,7] Therefore, the eventual goal should be primary prevention of hyperuricemia; for the promotion of this goal, risk factors in the chain of causation must be identified. The availability of accurate data on the incidence of hyperuricemia and SUA trend should enable planners of health care to focus on primary as well as secondary prevention efforts for the highest risk groups.

The aim of our longitudinal population study based on annual health examinations in the workplace was to identify the risk factors related to hyperuricemia by estimating the risk of incidence of hyperuricemia and SUA trend among middle-aged Japanese men.

MATERIALS AND METHODS

Study Cohort

To evaluate the factors related to increases in SUA, a longitudinal study was conducted between 1990 and 1998 among employees of T Corporation, one of the biggest building contractors in Osaka. The

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Industrial Safety and Health Law in Japan requires the employer to conduct annual health examinations of all employees; the employee data, which are anonymized, are available for research with the approval of the employer. The surveillance population consisted of 1,539 Japanese male office workers aged 30 to 52 years in May 1990. During the initial examination, fasting blood samples were drawn from an antecubital vein. SUA concentrations were determined by Nihon Clinical Laboratories Inc (Tokyo, Japan) by means of the uricase method[8] using an Olympus AU-5000 for 1990 through 1994 and an Olympus AU-5200 for 1995 through 1998 (Olympus Japan Co, Tokyo, Japan). Quality control of the laboratory was maintained internally, and the interassay and intraassay coefficients of variation for SUA were within 3% during the entire survey period. Hyperuricemia was defined as an SUA level of ≥7.5 mg/dL. Each subject's medical history and history of use of prescribed drugs were assessed by the examining physicians. Of 1,539 subjects, 162 (10.5%) were hyperuricemic at the initial examination. For 15 subjects (1.0%) who had been undergoing medical care for hyperuricemia, normouricemic values were recorded. Of the 1,362 subjects who had received no medical treatment for hyperuricemia and were identified as normouricemic during the initial examination, 50 (3.7%) were taking medication for hypertension and were removed from the cohort because of the possible effect of such medication on SUA levels.[3,9-12] The remaining 1,312 subjects constituted the study cohort. Subjects who were found to have become hyperuricemic during repeat surveys through May 1998 were defined as new incidences of hyperuricemia. Four subjects who were given antihyperuricemic drugs during the observation period were also considered new incidence cases. Of the study cohort, 9 consecutive SUA values were available for 1,106 men (84.3%). Of 1,106 subjects, 44 started medication for hyperuricemia or hypertension during the observation period.

Study Items

The health examinations at study entry and during repeat surveys consisted of a questionnaire, physical examinations, and collection of fasting blood samples for laboratory analysis. Data on alcohol intake and smoking habits were obtained by interview. An interviewer assessed the usual weekly intake of alcohol in a volume unit of "go" (a traditional Japanese unit of measurement for sake, corresponding to 23 g of ethanol), which was converted to grams of ethanol per day. One go is 180 mL of sake and corresponds to 1 bottle (663 mL) of beer, 2 single shots (75 mL) of whiskey, or 2 glasses (180 mL) of wine. The questionnaire asked about smoking habits (never, past, or current smoker); past or current smokers were asked about the number of cigarettes smoked daily and the duration of smoking in years. In this study, past and never smokers were combined, and the number of cigarettes smoked daily was used in the analysis. Weight and height were measured with the subjects wearing typical indoor clothing but with their shoes off. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Blood pressure was measured to the nearest 2 mm Hg with a standard sphygmomanometer on the right arm of subjects sitting after 5 minutes' rest. Korotkoff phases I and V were taken to present systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively. Total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, total protein, and blood urea nitrogen (BUN) were determined with the aid of an Olympus AU-5000 for 1990 through 1994 and an Olympus AU-5200 for 1995 through 1998. Hemoglobin A_{1c} (HbA_{1c}) was measured with an automated glycohemoglobin analyzer system HS-8 (Jookoo Co, Tokyo, Japan), and hematocrit and white blood cell levels were determined using an auto analyzer Sysmex E-4000 (Toa Medical Electronics Co, Tokyo, Japan).

Analytic Procedures

For each participant, person-years of follow-up were calculated from the date of enrollment to the date of diagnosis of hyperuricemia or the date of follow-up, whichever came first. The follow-up rate was 94.7% of the total potential person-years of follow-up. The Kaplan-Meier method[13] was used to estimate the cumulative incidence of hyperuricemia according to characteristics identified from baseline data, and the log-rank test was used to assess the significance of the unadjusted differences among the incidence curves. For the Kaplan-Meier analysis, data on the characteristics at study entry were subdivided into terciles (Table 1). The Cox proportional-hazards model[14] was used to evaluate the age-adjusted or multivariate relationships between the characteristics at entry and the development of hyperuricemia. To represent an individual's SUA trend during 1990 and 1998, each consecutive individual's 9 SUA values were regressed on the time of survey with a simple linear regression model, and the slope of coefficient of this model was used. The slopes for BMI, alcohol intake, cigarettes smoked, and blood samples were calculated similarly. Multiple linear regression analysis was performed to examine an independent association of factors and their relative importance as determinants of SUA slope. In the statistical analyses, log transformation was used for continuous variables (triglycerides) when necessary to obtain a normal distribution of data.

Data analysis was performed with the SPSS/PC statistical package (Marija J. Norusis/SPSS Inc., Chicago, IL). All reported *P* values are 2-tailed, and $P < .05$ was considered statistically significant.

RESULTS

Table 1 shows the estimated incidence rates of hyperuricemia over 8 years according to characteristics at study entry determined by use of the Kaplan-Meier method. The estimated incidence of hyperuricemia increased with increases in BMI, triglyceride level, SUA level, total protein level, white blood cell count, and alcohol intake. The incidence curves for the 3 terciles of each variable attained statistical significance on the basis of the log-rank test result. The estimated incidence rates were higher for those with DBP of ≥76 mm Hg and a BUN level of <13.9 mg/dL than for those with DBP of <76 mm Hg and a BUN level of ≥13.9 mg/dL. The curves for the terciles of these variables achieved statistical significance as determined by the log-rank test. The estimated incidence rates were higher for those younger than 44.8 years and with SBP of ≥122 mm Hg than for those aged 44.8 years or older and with SBP <122 mm Hg, but the curves for the terciles of these variables did not differ significantly among the terciles. The estimated incidence of hyperuricemia tended to increase as total cholesterol level increased and HbA_{1c} level decreased, but these incidence curves did not differ significantly among the terciles. There were no marked correlations between the incidence of hyperuricemia and HDL cholesterol level, hematocrit level, and smoking habits.

Table 2 shows the age-adjusted hazard ratios (HRs) for the incidence of hyperuricemia according to characteristics at study entry determined by the Cox proportional-hazards model. Significantly positive associations with the incidence of hyperuricemia were shown for BMI, SBP, DBP, total cholesterol level, log triglyceride level, SUA level, total protein level, white blood cell count, and alcohol intake. On the other hand, the HbA_{1c} level showed a significant negative association with the incidence of hyperuricemia. There were no significant correlations between the incidence of hyperuricemia and HDL cholesterol level, BUN level, hematocrit level, or smoking habits.

To determine the independent risk factors related to the incidence of hyperuricemia, the variables shown as statistically

Table 1. Cumulative Incidence Rates of Hyperuricemia Over 8 Years According to Characteristics at Study Entry Assessed by Kaplan-Meier Method

Variable	Subclass	n	%	95% CI
Age (yr)	30.0–40.3	432	21.4	17.4–25.4
	40.1–44.7	441	21.4	17.5–25.3
	44.8–52.9	439	15.8	12.3–19.3
BMI (kg/m^2)	≤22.0	438	13.4	10.1–16.7‡
	22.1–24.0	439	18.9	15.2–22.7
	≥24.1	435	26.0	21.8–30.3
SBP (mm Hg)	≤120	410	16.2	12.5–19.9
	122–132	399	21.9	17.7–26.1
	≥134	503	20.2	16.6–23.8
DBP (mm Hg)	≤74	432	14.5	11.1–18.0†
	76–82	390	21.9	17.7–26.1
	≥84	490	21.9	18.1–25.6
Total cholesterol (mg/dL)	≤182	430	17.4	13.7–21.1
	183–212	443	19.6	15.8–23.4
	≥213	439	21.5	17.5–25.4
HDL cholesterol (mg/dL)	≤49	410	18.7	14.8–22.7
	50–61	442	22.0	18.0–26.0
	≥62	460	17.8	14.2–21.3
Triglyceride (mg/dL)	≤82	430	12.1	8.9–15.2‡
	83–131	442	21.6	17.7–25.6
	≥132	440	24.6	20.5–28.8
Uric acid (mg/dL)	≤5.0	404	4.4	2.3–6.4‡
	5.1–6.0	439	9.0	6.2–11.8
	6.1–7.4	469	42.1	37.5–46.7
Total protein (g/dL)	≤7.2	377	16.8	12.9–20.8*
	7.3–7.6	498	18.2	14.7–21.7
	≥7.7	437	23.2	19.2–27.3
HbA_{1c} (%)	≤4.9	381	21.6	17.5–25.7
	5.0–5.3	442	19.2	15.2–23.1
	≥5.4	489	17.8	14.3–21.3
BUN (mg/dL)	≤13.8	435	23.7	19.5–27.8*
	13.9–16.7	439	17.8	14.1–21.5
	≥16.8	438	17.1	13.5–20.7
Hematocrit (%)	≤45.0	423	20.1	16.1–24.0
	45.1–47.1	427	18.6	14.8–22.3
	≥47.2	462	19.8	16.1–23.6
White blood cell ($\times 10^2/\mu$L)	≤55.9	420	15.6	11.7–19.5†
	56.0–69.9	453	19.2	10.6–17.5
	≥70.0	439	23.5	19.4–27.6
Alcohol intake (g/d of ethanol)	None	505	14.0	9.2–18.8‡
	≤45.9	550	20.1	16.9–23.3
	≥46.0	257	28.8	25.2–32.4
Smoking (cigarettes/d)	None	565	21.0	18.1–24.0
	≤29	478	17.8	13.0–22.6
	≥30	269	19.1	14.4–23.8

NOTE. The difference between the curves was measured by the log-rank test. n = 1,312.

*$P < .05$.

†$P < .01$.

‡$P < .001$.

significant in the age-adjusted analyses were included in the multivariate model. DBP was used as an index of blood pressure because DBP was closely associated with SBP ($r = .740$, $P < .001$). Two separate analyses were carried out, one using the model not including the SUA level and the other including the SUA level (Table 3). When the SUA level was not included as a factor in the model, BMI, log triglyceride level, white blood cell count, and alcohol intake showed significantly positive associations with the incidence of hyperuricemia, whereas age and HbA_{1c} level showed significantly negative associations. In the model including the SUA level, the adjusted HR for an increase of 1 SD (1.12 mg/dL) in the SUA level was 4.40 (95% confidence interval [CI], 3.56 to 5.45). BMI, white blood cell count, and alcohol intake remained significant positive factors. The adjusted HRs for increases of 1 SD (2.64 kg/m^2) in BMI, 1 SD (18.0×10^2 counts/μL) in the white blood cell count, and 1 SD (25.3 g/d of ethanol) in alcohol intake were 1.16 (95% CI, 1.01 to 1.33), 1.14 (95% CI, 1.01 to 1.28), and 1.26 (95% CI, 1.11 to 1.42), respectively. Age, log triglyceride level, and HbA_{1c} level were no longer independent predictive factors when the SUA level was included as a factor in the model.

Table 4 shows the age-adjusted standardized coefficients of SUA slope determined by multiple linear regression analyses in 1,062 subjects for whom 9 consecutive SUA values were available and who did not start medication for hyperuricemia or hypertension during the observation period. The SUA slope was significantly negatively related to BMI, DBP, total cholesterol level, log triglyceride level. SUA level, HbA_{1c} level, BUN level, and hematocrit level at study entry. On the other hand, the SUA slope was significantly positively correlated with white blood cell count and alcohol intake. As for the slopes of selected variables, the SUA slope was significantly positively correlated with the slopes of BMI, SBP, DBP, total cholesterol, log triglyceride, total protein, BUN, and hematocrit. The SUA slope was significantly negatively correlated with HbA_{1c} slope.

Table 5 shows the results of stepwise linear regression anal-

Table 2. Age-Adjusted HRs for Incidence of Hyperuricemia Over 8 Years for Selected Variables at Study Entry Assessed by Cox Proportional-Hazards Model

Variable	HR	95% CI
BMI (increase of 2.64 kg/m^2)	1.31‡	1.16–1.47
SBP (increase of 14.5 mm Hg)	1.16*	1.02–1.31
DBP (increase of 10.5 mm Hg)	1.21†	1.07–1.37
Total cholesterol (increase of 33.9 mg/dL)	1.16*	1.03–1.31
HDL cholesterol (increase of 13.5 mg/dL)	0.90	0.79–1.03
Log triglyceride (increase of 0.541 mg/dL in $\log_e$)	1.28‡	1.14–1.44
Uric acid (increase of 1.12 mg/dL)	4.59‡	3.73–5.64
Total protein (increase of 0.39 g/dL)	1.16*	1.03–1.32
HbA_{1c} (increase of 0.63%)	0.85*	0.73–0.98
BUN (increase of 3.52 mg/dL)	0.93	0.81–1.06
Hematocrit (increase of 2.8%)	1.04	0.91–1.18
White blood cell (increase of $18.0 \times 10^2/\mu$L)	1.18†	1.06–1.33
Alcohol intake (increase of 25.3 g/d of ethanol)	1.38*	1.22–1.56
Smoking (increase of 16.8 cigarettes/d)	1.05	0.91–1.21

NOTE. HR for an increase of 1 SD; value of 1 SD given in parentheses.

*$P < .05$.

†$P < .01$.

‡$P < .001$.

Table 3. Multivariate HRs for Incidence of Hyperuricemia Over 8 Years for Selected Variables at Study Entry Assessed by Cox Proportional-Hazards Model

Variable	Not Including Serum Uric Acid Level		Serum Uric Acid Level Included	
	HR	95% CI	HR	95% CI
Age (increase of 5 years)	0.86*	0.76–0.97	0.90	0.80–1.02
BMI (increase of 2.64 kg/m^2)	1.19†	1.04–1.35	1.16*	1.01–1.33
DBP (increase of 10.5 mm Hg)	1.09	0.95–1.25	1.04	0.90–1.19
Total cholesterol (increase of 33.9 mg/dL)	1.02	0.89–1.17	1.02	0.89–1.19
Log triglyceride (increase of 0.541 mg/dL in $\log_e$)	1.16*	1.01–1.33	0.92	0.80–1.06
Uric acid (increase of 1.12 mg/dL)	—		4.40‡	3.56–5.45
Total protein (increase of 0.39 g/dL)	1.09	0.96–1.24	0.99	0.86–1.13
HbA_{1c} (increase of 0.63%)	0.83*	0.72–0.96	0.88	0.76–1.03
White blood cell (increase of 18.0 $\times$ 10^2/μL)	1.15*	1.03–1.30	1.14*	1.01–1.28
Alcohol intake (increase of 25.3 g/d of ethanol)	1.33‡	1.18–1.51	1.26‡	1.11–1.42

NOTE. HR for an increase of 1 SD except age; value of 1 SD given in parentheses.
*$P < .05$.
†$P < .01$.
‡$P < .001$.

yses for SUA slope on the variables shown as statistically significant in Table 4. The DBP slope was used as an index of blood pressure slope because it was closely associated with SBP slope ($r = .631$, $P < .001$). Two separate analyses were carried out, one using the model not including the baseline SUA level and the other including the baseline SUA level. When the baseline SUA level was not included as a factor in the model, independent and significant correlates with SUA slope were, in order of relative importance, slopes of BMI, HbA_{1c} (negative), BUN, log triglyceride, and total protein and baseline levels of hematocrit (negative), white blood cells, and HbA_{1c}; 22.8% of the total variation in SUA slope was accounted for by these variables combined. In the model including the baseline SUA level, SUA level (negative) and alcohol intake at study entry emerged as statistically significant, and the cumulative percentage of variation for the SUA slope was 25.6%.

Table 4. Age-Adjusted Standardized Coefficients of SUA Slope Over 8 Years in 1,062 Men, Determined by Multiple Linear Regression Analyses

Variable	At Study Entry	Slopes Over 8 Years
BMI (kg/m^2)	−0.100†	0.322‡
SBP (mm Hg)	−0.049	0.101†
DBP (mm Hg)	−0.108‡	0.102‡
Total cholesterol (mg/dL)	−0.067*	0.172‡
High-density lipoprotein cholesterol (mg/dL)	0.030	−0.048
Log triglyceride (mg/dL)	−0.089†	0.241‡
Uric acid (mg/dL)	−0.171‡	—
Total protein (g/dL)	−0.047	0.136‡
HbA_{1c} (%)	−0.092†	−0.269‡
BUN (mg/dL)	−0.096†	0.164‡
Hematocrit (%)	−0.133‡	0.096†
White blood cell ($\times$ 10^2/μL)	0.070*	−0.041
Alcohol intake (g/d of ethanol)	0.069*	−0.035
Smoking (cigarettes/d)	−0.043	0.041

*$P < .05$.
†$P < .01$.
‡$P < .001$.

DISCUSSION

In the present study, the highest cumulative rate of incidence of hyperuricemia over 8 years was observed among those who had high-normal SUA levels of 6.1 to 7.4 mg/dL initially (42.1%, 95% CI, 37.5% to 46.7%). The adjusted HR for an increase of 1 SD (1.12 mg/dL) in the SUA level was 4.40 (95% CI, 3.56 to 5.45). Choosing a cut-off point to define hyperuricemia is an arbitrary decision, complicated by the fact that SUA levels vary according to methods or populations. However, our findings suggest that a high-normal SUA level appears to be an important issue in health management of middle-aged Japanese men.

A number of epidemiologic studies have determined that absolute and relative weight and alcohol intake are determinants of SUA levels.[15-20] Our study found that BMI and alcohol intake at study entry and BMI slope were independent risk factors for the development of increased SUA levels, even when adjustments were made for other metabolic disorders. Considering the beneficial effects of weight loss and cessation of alcohol intake on uric acid,[21,22] promotion of a health education program at the workplace for appropriate body weight and alcohol consumption may be important for primary prevention of increased SUA levels for this population.

As for other biologic and behavioral factors for hyperuricemia, metabolic disorders such as hypertriglyceridemia, low HDL cholesterolemia, non–insulin-dependent diabetes mellitus, and hypertension are frequently observed among individuals with hyperuricemia.[4,6,23-25] These disorders frequently cluster within the same individual in "syndrome X" or "insulin resistance syndrome," and a high SUA concentration has been listed among the components of the insulin resistance syndrome.[26-28] The observations that insulin stimulates the tubular sodium-hydrogen exchanger and exerts a direct effect on increasing renal sodium reabsorption have led to the proposal of a unifying hypothesis that links hyperuricemia, low urinary uric acid excretion, and decreased glucose use, ie, insulin resis-

Table 5. Stepwise Linear Regression Analyses of Serum Uric Acid Slope Over 8 Years

Variables	Natural Coefficient	Standardized Coefficient	T value	Cumulative R^2*
Model not including serum uric acid level				
Slope of BMI (kg/m^2/yr)	0.114	0.204	43.63§	0.101
Slope of HbA_{1c} (%/yr)	−0.227	−0.238	70.99§	0.149
Slope of BUN (mg/dL/yr)	0.050	0.183	45.46§	0.181
Slope of log triglyceride (mg/dL/yr)	0.258	0.139	21.57§	0.201
Slope of total protein (g/dL/yr)	0.257	0.106	14.95§	0.212
Hematocrit at study entry (%)	−0.003	−0.092	10.54‡	0.217
White blood cell at study entry ($\times 10^2/\mu L$)	0.048×10^{-2}	0.093	10.96‡	0.224
HbA_{1c} at study entry (%)	−0.010	−0.068	5.81†	0.228
Model with serum uric acid level included				
Slope of BMI (kg/m^2/yr)	0.113	0.202	44.39§	0.101
Slope of HbA_{1c} (%/yr)	−0.216	−0.226	65.78§	0.149
Slope of BUN (mg/dL/yr)	0.050	0.184	47.60§	0.181
Uric acid (mg/dL)	−0.014	−0.161	35.50§	0.204
Slope of log triglyceride (mg/dL/yr)	0.258	0.139	22.30§	0.224
Slope of total protein (g/dL/yr)	0.260	0.107	15.89§	0.235
Alcohol intake (g/d of ethanol)	0.027×10^{-2}	0.070	6.75†	0.240
HbA_{1c} at study entry (%)	−0.012	−0.080	8.09‡	0.245
White blood cell at study entry ($\times 10^2/\mu L$)	0.048×10^{-2}	0.092	11.10‡	0.251
Hematocrit at study entry (%)	−0.003	−0.075	7.30†	0.256

*Percentage of variation accounted for = $R^2 \times 100$. R, multiple correlation.
†$P < .05$.
‡$P < .01$.
§$P < .001$.

tance.[29,30] Although not many population studies have addressed the relation between triglyceride and SUA, a strong positive correlation between triglyceride and SUA levels has been demonstrated.[17,18,24] Diabetic patients generally have lower levels of SUA than those without diabetes,[15-18,24,25] whereas higher levels of SUA have been observed among those with prediabetic status or impaired glucose tolerance.[16,17,20,31] Furthermore, some studies have suggested that creatinine is a major determinant of SUA levels.[15-17] However, epidemiologic evidence regarding SUA is conflicting as to the relationship of SUA levels to total cholesterol, HDL cholesterol, untreated hypertension, and smoking habits.[15-20,23,24,31] In this study, the baseline log triglyceride level and the slopes of BUN, log triglyceride, and total protein were significantly associated with the development of increased SUA levels. On the other hand, baseline HbA_{1c} level and HbA_{1c} slope were significantly inversely associated with the development of increased SUA levels. Thus, our findings highlight the clinical importance of determining hyperuricemia in subjects with other metabolic disorders and vice versa.

White blood cell count was significantly associated with the development of increased SUA levels, even when SUA level was included as a factor in the model. Characteristically, purine overproduction occurs in myeloid and lymphoid proliferative disorders.[32-34] An increase in the proliferation rate of cells of any type may increase purine synthesis and degradation, so that the miscible SUA pool may enlarge, leading to hyperuricemia. Further investigations are needed to identify whether the white blood cell count plays a causative role in the development of increased SUA levels among healthy people.

In this study, age was significantly negatively associated with the incidence of hyperuricemia and showed a weak but significantly negative association with BMI slope ($r = -.110$, $P < .001$). The negative association of age with the development of hyperuricemia may be partly explained by a larger weight gain among younger workers. Baseline hematocrit level was also negatively associated with SUA slope. The hematocrit level was significantly correlated with the baseline SUA level ($r = .139$, $P < .001$) and SUA slope ($r = -.164$, $P < .001$) and showed a highly negative association with hematocrit slope ($r = -.397$, $P < .001$). These results suggest that a random effect in a subject who in general has relatively high or low values contributes to the negative association between the baseline hematocrit level and SUA slope.

There are several limitations to our study. Identification of incidence cases of elevated SUA levels is one problem in conducting longitudinal studies of this common condition. We are aware of the limitations implied in our dependence on annual measurements of SUA to define persons at risk and those developing elevated levels of SUA.

Another limitation is that the normouricemic cohort in this study may not be typical of the general population. Individuals whose SUA or blood pressure levels were already elevated when they were younger or who reported having undergone treatment for hyperuricemia or hypertension were excluded from this survey. Thus, a healthy worker effect may exist in this study.

The third problem concerns the study participants lost to follow-up during the course of the study. In this study, cases that were not followed up did not differ from other cases with respect to age and baseline levels and slopes of BMI, blood pressure, blood sample data, alcohol intake, or smoking habits. Therefore, we believe the influence of cases not followed up on estimations of the incidence of hyperuricemia and SUA trend was not very strong.

Despite these potential limitations, our findings from a cohort of middle-aged Japanese men support the concept that obesity, alcohol consumption, and multimetabolic disorders are strong predictors of the risk of development of hyperuricemia. Our data also indicate that the white blood cell count may be a contributory factor in the incidence of hyperuricemia.

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REFERENCES

1. Ueshima H: Changes in dietary habits, cardiovascular risk factors and mortality in Japan. Acta Cardiol 45:311–327, 1990
2. Scott JT: Asymptomatic hyperuricaemia. Br Med J 294:987–988, 1987
3. Roubenoff R: Gout and hyperuricemia. Rheum Dis Clin North Am 16:539–550, 1990
4. Campion EW, Glynn RJ, DeLabry LO: Asymptomatic hyperuricemia: Risks and consequences in the Normative Aging Study. Am J Med 82:421–426, 1987
5. Brand FN, McGee DL, Kannel WB, et al: Hyperuricemia as a risk factor of coronary heart disease: The Framingham Study. Am J Epidemiol 121:11–18, 1985
6. Freedman DS, Williamson DF, Gunter EW, et al: Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I Epidemiologic Follow-up Study. Am J Epidemiol 141:637–644, 1995
7. Singer JZ, Wallace SL: The allopurinol hypersensitivity syndrome: Unnecessary morbidity and mortality. Arthritis Rheum 29:82–87, 1986
8. Kabasakalian P, Kalliney S, Westcott A: Determination of uric acid in serum, with use of uricase and a tribromophenol-aminoantipyrine chromogen. Clin Chem 19:522–524, 1973
9. Faulds D, Sorkin EM: Felodipine: A review of the pharmacology and therapeutic use of the extended release formulation in older patients. Drugs Aging 2:374–388, 1992
10. Iimura O, Shimamoto K: Efficacy and mode of action of manidipine: A new calcium antagonist. Am Heart J 125:635–641, 1993
11. Tsunoda K, Abe K, Hagino T, et al: Hypotensive effect of losartan, a nonpeptide angiotensin II receptor antagonist, in essential hypertension. Am J Hypertens 6:28–32, 1993
12. van Buren M, Bijlsma JA, Boer P, et al: Natriuretic and hypotensive effect of adenosine-1 blockade in essential hypertension. Hypertension 22:728–734, 1993
13. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457–481
14. Cox DR: Regression models and life-tables. J R Stat Soc [B] 34:187–200, 1972
15. Okada M, Ueda K, Omae T, et al: The relationship of serum uric acid to hypertension and ischemic heart disease in Hisayama population, Japan. J Chron Dis 35:173–178, 1982
16. Tuomilehto J, Zimmet P, Wolf E, et al: Plasma uric acid level and its association with diabetes mellitus and some biologic parameters in a biracial population of Fiji. Am J Epidemiol 127:321–336, 1988
17. Kono S, Shinchi K, Imanishi K, et al: Behavioural and biological correlates of serum uric acid: A study of self-defence officials in Japan. Int J Epidemiol 23:517–522, 1994
18. Yano K, Rhoads GG, Kagan A: Epidemiology of serum uric acid among 8000 Japanese-American men in Hawaii. J Chron Dis 30:171–184, 1977
19. Goldbourt U, Medalie JH, Herman JB, et al: Serum uric acid: correlation with biochemical, anthropometric, clinical and behavioral parameters in 10,000 Israeli men. J Chron Dis 33:435–443, 1980
20. Cook DG, Shaper AG, Thelle DS, et al: Serum uric acid, serum glucose and diabetes: Relationships in a population study. Postgrad Med J 262:1001–1006, 1986
21. Nicholls A, Scott JT: Effect of weight-loss on plasma and urinary levels of uric acid. Lancet 2:1223–1224, 1972
22. Faller J, Fox IH: Ethanol-induced hyperuricemia: Evidence for increased urate production by activation of adenine nucleotide turnover. N Engl J Med 307:1598–1602, 1982
23. Klein R, Klein BE, Cornoni JC, et al: Serum uric acid. Its relationship to coronary heart disease risk factors and cardiovascular disease, Evans County, Georgia. Arch Intern Med; 132:401–410, 1973
24. Zalokar J, Lellouch J, Claude JR, et al: Epidemiology of serum uric acid and gout in Frenchmen. J Chron Dis 27:59–75, 1974
25. Goldbourt U, Medalie JH, Herman JB, et al: Serum uric acid: Correlation with biochemical, anthropometric, clinical and behavioral parameters in 10,000 Israeli men. J Chron Dis 33:435–443, 1980
26. Reaven GM: Banting lecture: Role of insulin resistance in human disease. Diabetes 37:1595–1607, 1988
27. Zavaroni I, Bonora E, Pagliara M, et al: Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. N Engl J Med 320:702–706, 1989
28. Cigolini M, Targher G, Tonoli M, et al: Hyperuricaemia: Relationships to body fat distribution and other components of the insulin resistance syndrome in 38-year-old healthy men and women. Int J Obes 19:92–96, 1995
29. Ward HJ: Uric acid as an independent risk factor in the treatment of hypertension. Lancet 352:670–671, 1998
30. Puig JG, Ruilope LM: Uric acid as a cardiovascular risk factor in arterial hypertension. J Hypertens 17:869–872, 1999
31. Herman JB, Goldbourt U: Uric acid and diabetes: Observations in a population study. Lancet 2:240–243, 1982
32. Rieselbach RE, Bentzel CJ, Cotlove E, et al: Uric acid excretion and renal function in the acute hyperuricemia of leukemia: Pathogenesis and therapy or uric acid nephropathy. Am J Med 37:872–884, 1964
33. DeConti RC, Calabresi P: Use of allopurinol for prevention and control of hyperuricemia in patients with neoplastic disease. N Engl J Med 274:481–486, 1966
34. Cohen LF, Balow JE, Magrath IT, et al: Acute tumor lysis syndrome. A review of 37 patients with Burkitt's lymphoma. Am J Med 68:486–491, 1980