

## The Incidence of Hyperuricemia and Correlated Factors in Middle-Aged Japanese Men

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**Abstract: The Incidence of Hyperuricemia and Correlated Factors in Middle-Aged Japanese Men: Noriyuki NAKANISHI, et al. Department of Social and Environmental Medicine, Course of Social Medicine, Osaka University Graduate School of Medicine F2**—To identify the factors responsible for increases in serum uric acid (SUA), 1,346 hyperuricemia-free (less than 7.5 mg/dl of SUA and no medication for hyperuricemia or hypertension) Japanese male office workers aged 30 to 53 yr were followed up for seven successive years with annual examinations, with an average period of observation of 6.4 yr with a standard deviation of 1.6 yr. Subjects who were found to have become hyperuricemic (SUA levels of 7.5 mg/dl or more) or who started medication for hyperuricemia during repeat survey were defined as incidence cases. An analysis by means of the Kaplan-Meier method showed that the incidence of hyperuricemia increased significantly with increases in the body mass index (BMI), systolic blood pressure, diastolic blood pressure, triglyceride level, SUA level, total protein level, white blood cell level, and alcohol intake. From the age-adjusted analysis with the Cox proportional hazards model, the total cholesterol level and hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) level emerged as significant positive and negative factors for the incidence of hyperuricemia, respectively. Multivariate analysis, excluding the SUA level as a factor in the Cox proportional hazards model, indicated that the BMI, Log triglyceride level, white blood cell level, and alcohol intake were significantly positively associated with the incidence of hyperuricemia. On the other hand, age and the HbA<sub>1c</sub> level were significantly inversely associated with the incidence of hyperuricemia. When the SUA level was included as a factor in the model, BMI and alcohol intake remained as independent

factors. Furthermore, the white blood cell level was identified as marginally significant for the incidence of hyperuricemia ( $p=0.064$ ). In conclusion, obesity and alcohol intake were determined to be independent predictors for the development of hyperuricemia. In addition, the white blood cell level may be a contributory factor.

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**Key words:** Incidence of hyperuricemia, Risk factors, Longitudinal study, Japanese men, Middle age

High serum uric acid (SUA) levels are causally associated with gout<sup>1–3</sup> and have been reported to be a risk factor for coronary heart disease<sup>2–5</sup>. Although secondary prevention with the focus on diagnosis and treatment of hyperuricemia is the goal of current medical efforts, long-term antihyperuricemic therapy involves both high costs and risks<sup>1,6</sup>. Therefore, the eventual goal should be the primary prevention of hyperuricemia, for the promotion of which risk factors in the chain of causation have to be identified. The availability of accurate data on incidence of hyperuricemia 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 at the workplace was to identify the risk factors related to hyperuricemia by estimating the risk of incidence of hyperuricemia among middle-aged Japanese men.

### Subjects and Methods

#### *Study cohort*

To evaluate the factors related to increases in SUA, a systematic surveillance of the risks of developing hyperuricemia was conducted between 1990 and 1997 among employees of T Corporation, which is one of the biggest building contractors in Osaka. All Japanese male

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office workers aged 30 to 53 yr in May 1990 were invited to attend a survey (N=1,577), and the participation rate was 100.0%. During the initial examination, fasting blood samples were drawn from an antecubital vein. SUA concentrations were determined by the Nihon Clinical Laboratories Inc. (Tokyo, Japan) by means of the uricase method<sup>7</sup>, with an Olympus AU-5000 (Olympus Japan Co., Ltd., Tokyo, Japan) for the period 1990–1994 and an Olympus AU-5200 for 1995–1997 (Olympus Japan Co., Ltd., 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 and over. The medical history and history of use of prescribed drugs of the subjects were assessed by the examining physicians. Of the total of 1,577 subjects, 166 (10.5%) were identified to be hyperuricemic at the initial examination. For 15 subjects (1.0%) who had been undergoing medical care for hyperuricemia, a normouricemic value was recorded. Of the 1,396 subjects who had had no medical treatment for hyperuricemia and who were identified as normouricemic during the initial examination, 50 (3.6%) who were taking medication for hypertension were removed from the cohort because of the possible effect of such medication on SUA levels<sup>3, 8–11</sup>. The remaining 1,346 subjects constituted the study cohort and were followed up for seven years with annual examinations until May 1997. Subjects who were found to have become hyperuricemic or who started medication for hyperuricemia during repeat surveys were defined as new incidences of hyperuricemia. Follow-up until May 1997 could be completed for only 1,159 subjects (86.1%), because 187 (13.9%) had transferred to another locality or had resigned or retired during the follow-up study. Of 187 subjects who could not be followed up until May 1997, 26 (13.9%) had SUA levels of 7.5 mg/dl or more and 4 (2.1%) were given antihyperuricemic drugs during the follow-up period. On the other hand, among 228 subjects who were identified as hyperuricemic cases during the follow-up period, 30 (16.0%) could not be followed up until the end of the follow-up.

#### *Study items*

The health examinations at entry consisted of a questionnaire, physical examinations, and collection of blood samples for laboratory analysis. Data on alcohol intake and smoking habits were obtained by interview. Alcohol consumption was measured by means of a quantity and frequency questionnaire and converted to the equivalent number of *go*, a traditional Japanese unit of volume for sake (1 *go*=180 ml and contains 23 g of ethanol). 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<sup>2</sup> (kg/m<sup>2</sup>). Blood pressure was measured to the nearest 2 mm Hg with a standard sphygmomanometer on the right arm of subjects sitting after 5 min 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 (Olympus Japan Co., Ltd., Tokyo, Japan). Hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) was determined with an automated glycohemoglobin analyzer HS-8 (Jookoo Co., Ltd., Tokyo, Japan), and hematocrit and white blood cell levels were determined with a Sysmex E-4000 auto analyzer (Toa Medical Electronics Co., Ltd., Tokyo, Japan). With respect to age, BMI, SBP, DBP, blood sample data, alcohol intake, and smoking habits at entry, the 187 cases which could not be followed up until May 1997 did not differ significantly from the 1,159 cases which could. Furthermore, among 228 cases which were identified as hyperuricemic, there were no significant differences in characteristics at entry between the 30 cases which could not be followed up until May 1997 and the 198 cases which could.

#### *Analytic procedures*

The observation times were calculated by using the date of the initial examination and the date of the incidence of hyperuricemia or the date of follow-up (the eighth examination), or the date of the last registration in T Corporation, Osaka. Those who had been transferred to another locality or had resigned or retired during the follow-up period have censored observation times as do those members of the cohort who were still in T Corporation, Osaka, at the end of the follow-up. The mean observation period of this cohort was 6.4 yr with a standard deviation (SD) of 1.62 yr, and the mean (SD) number of times of SUA measurement, including the initial examination, was 7.3 (1.59). The Kaplan-Meier method<sup>12</sup> was used to estimate the cumulative incidence of hyperuricemia according to the 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 entry were subdivided into terciles and the values for percentiles were 33.3 and 36.7 except for drinking alcohol and smoking (Table 1). The Cox proportional hazards model<sup>13</sup> was used to evaluate the age-adjusted or multivariate relations between the characteristics at entry and the development of hyperuricemia. For the analyses with the Cox proportional hazards model, Log transformation was used for continuous variables when necessary (triglycerides) to obtain a normal distribution of data. For discrete variables, hazard ratio (HR) estimates compared with the reference level of each subclass were calculated by

creating two dummy variables for each variable as follows:  $x_1=0$ ,  $x_2=0$  for the reference level;  $x_1=1$ ,  $x_2=0$  for the second level, and  $x_1=0$ ,  $x_2=1$  for the third level.

Data analysis was performed with the SPSS/PC statistical package (Marija J. Norusis/ SPSS Inc., Chicago, IL, USA). All reported *p* values are two-tailed and  $p < 0.05$  was considered statistically significant.

## Results

Table 1 shows the estimated incidence rates of hyperuricemia over seven years determined with the Kaplan-Meier method. The estimated incidence of hyperuricemia increased with increases in BMI, SBP, DBP, the triglyceride level, SUA level, total protein level, white blood cell level, and alcohol intake. The incidence curves for the three tertiles of each variable attained statistical significance on the basis of the log-rank test result. The estimated incidence rate was higher for those with a BUN level of less than 14.0 mg/dl than for those with a BUN level of 14.0 mg/dl and over, and the curves for the tertiles of this variable achieved statistical significance as determined by the log-rank test. The estimated incidence of hyperuricemia tended to increase as the total cholesterol level increased, but these incidence curves did not differ significantly among the tertiles. The estimated incidence rate was lower for those aged 45.2 to 53.9 yr than for those aged less than 45.2 yr, but the incidence curves did not differ significantly among the tertiles. There were no marked correlations between the HDL cholesterol level, HbA<sub>1c</sub> level, hematocrit level and smoking habits and the incidence of hyperuricemia.

Table 2 shows the age-adjusted HRs for the incidence of hyperuricemia determined with the Cox proportional hazards model. Significantly positive associations with the incidence of hyperuricemia were shown for BMI, SBP, DBP, the total cholesterol level, Log triglyceride level, SUA level, total protein level, white blood cell level, and alcohol intake. On the other hand, the HbA<sub>1c</sub> level showed a significant negative association with the incidence of hyperuricemia. There were no significant correlations between the HDL cholesterol level, BUN level, hematocrit level and smoking habits and the incidence of hyperuricemia.

To determine the independent risk factors related to the incidence of hyperuricemia, the variables shown as statistically significant in the age-adjusted analysis were included in a multivariate model. DBP was used as an index of blood pressure, because DBP was closely associated with SBP ( $r=0.742$ ,  $p < 0.001$ ). Two separate analyses were carried out, one using the model not including the SUA level and the other with the SUA level included (Table 3). When the SUA level was not included as a factor in the model, BMI, the Log triglyceride level, white blood cell level and alcohol intake showed significantly positive associations with the incidence of

hyperuricemia, whereas age and the HbA<sub>1c</sub> 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 4.35 [95% confidence interval (CI): 3.49–5.43]. BMI and alcohol intake remained significant positive factors. The adjusted HR for an increase of 1 SD (2.63 kg/m<sup>2</sup>) in BMI was 1.16 (95% CI: 1.01–1.34), and the adjusted HRs for less than 2.0 go/day and for 2.0 go/day or more of alcohol consumption, compared with non-consumption of alcohol, were 1.44 (95% CI: 1.04–1.99) and 1.86 (95% CI: 1.31–2.63), respectively. The Log triglyceride level and white blood cell level were no longer independent predictive factors when the SUA level was included as a factor in the model, although the adjusted HR for an increase of 1 SD ( $18.0 \times 10^2$  counts/mm<sup>3</sup>) in the white blood cell level was 1.13 (95% CI: 0.99–1.28,  $p=0.064$ ).

## Discussion

In the present study, the highest cumulative rate of the incidence of hyperuricemia over 7 yr was observed among those who had a high-normal SUA level of 6.2 to 7.4 mg/dl initially (40.1%, 95% CI: 35.5–44.6%). The adjusted HR for an increase of 1 SD (1.12 mg/dl) in the SUA level was 4.35 (95% CI: 3.49–5.43). Choosing a cut-off point to define hyperuricemia is an arbitrary decision, complicated by the fact that SUA levels vary according to the methods or populations<sup>14, 15</sup>, but our findings suggest that a high-normal SUA level is an important issue in the health management of middle-aged Japanese men.

A number of epidemiological studies have determined that both absolute and relative weight and alcohol intake are determinants of SUA levels<sup>15–21</sup>. Our study demonstrated that BMI and alcohol intake were independent risk factors for the incidence of hyperuricemia even when adjustments were made for other metabolic disorders. Considering the beneficial effects of weight-loss and a cessation of alcohol intake on uric acid<sup>22, 23</sup>, promotion of a health education program at the workplace for appropriate body weight and alcohol consumption may well be important for primary prevention of hyperuricemia for this population.

As for other biological 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<sup>1, 5, 24–26</sup>. 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<sup>18, 19, 25</sup>. Diabetics generally have lower levels of SUA than non-diabetics<sup>16–19, 25, 26</sup>, whereas higher levels of SUA have been observed among those with prediabetic status or

**Table 1.** Cumulative incidence rates of hyperuricemia over a 6.4-yr period on average according to characteristics at entry assessed by the Kaplan-Meier method

Variables	Subclass	n=1,346	%	95% confidence interval†
Age group (yr)	30.0–40.4	446	18.8	15.2–22.5
	40.5–45.1	449	18.5	14.9–22.1
	45.2–53.9	451	13.5	10.4–16.7
Body mass index (kg/m <sup>2</sup> )	≤22.0	448	11.2	8.2–14.1***
	22.1–24.0	451	16.4	13.0–19.8
	≥24.1	447	23.3	19.4–27.2
Systolic blood pressure (mmHg)	≤122	475	13.7	10.6–16.8*
	124–134	424	17.7	14.1–21.3
	≥136	447	19.7	16.0–23.4
Diastolic blood pressure (mmHg)	≤76	535	13.6	10.7–16.5**
	78–84	403	16.4	12.8–20.0
	≥86	408	21.8	17.8–25.8
Total cholesterol (mg/dl)	≤183	447	14.5	11.3–17.8
	184–212	447	17.2	13.7–20.7
	≥213	452	19.0	15.4–22.7
High-density lipoprotein cholesterol (mg/dl)	≤49	413	16.0	12.5–19.5
	50–61	457	18.4	14.8–21.9
	≥62	476	16.4	13.1–19.7
Triglyceride (mg/dl)	≤82	438	10.1	7.2–12.9***
	83–132	458	18.3	14.8–21.9
	≥133	450	22.2	16.4–28.0
Uric acid (mg/dl)	≤5.1	470	3.4	1.8– 5.0***
	5.2–6.1	439	8.4	5.8–11.0
	6.2–7.4	437	40.1	35.5–44.6
Total protein (g/dl)	≤7.3	505	13.5	10.5–16.4*
	7.4–7.6	394	17.5	13.8–21.3
	≥7.7	447	20.4	16.6–24.1
HbA <sub>1c</sub> (%)	≤4.9	456	17.8	14.3–21.3
	5.0–5.3	388	17.8	14.0–21.6
	≥5.4	502	15.5	12.4–18.7
Blood urea nitrogen (mg/dl)	≤13.9	445	20.5	16.7–24.2*
	14.0–16.7	452	14.8	11.5–18.1
	≥16.8	449	15.6	12.2–18.9
Hematocrit (%)	≤45.0	433	17.3	13.8–20.9
	45.1–47.2	462	15.8	12.5–19.1
	≥47.3	451	17.7	14.2–21.3
White blood cell (× 10 <sup>2</sup> /mm <sup>3</sup> )	≤55.9	427	14.7	11.5–17.9*
	56.0–69.9	468	15.0	12.0–18.0
	≥70.0	451	21.1	17.7–24.4
Drinking alcohol (go/day)	None	516	12.0	9.2–14.8***
	≤1.9	568	17.1	14.0–20.2
	≥2.0	262	26.3	21.0–31.7
Smoking (cigarettes/day)	None	576	17.3	14.8–19.9
	≤29	493	17.2	12.6–21.7
	≥30	277	15.7	11.2–20.2

\*p<0.05; \*\*p<0.01; \*\*\*p<0.001 (log-rank test for the difference between the curves). †95% confidence interval for cumulative incidence rate.

**Table 2.** Age-adjusted hazard ratios for the incidence of hyperuricemia over a 6.4-yr period on average for selected variables at entry assessed by the Cox Proportional Hazards model

Variables	Hazard ratio	95% confidence interval†
Body mass index (increase of 2.63 kg/m <sup>2</sup> )‡	1.34***	1.19–1.51
Systolic blood pressure (increase of 14.6 mm Hg)‡	1.17*	1.03–1.33
Diastolic blood pressure (increase of 10.5 mm Hg)‡	1.27***	1.12–1.44
Total cholesterol (increase of 34.1 mg/dl)‡	1.20**	1.06–1.36
High-density lipoprotein cholesterol (increase of 13.5 mg/dl)‡	0.92	0.81–1.05
Log triglyceride (increase of 0.545 mg/dl in log <sub>e</sub> )‡	1.31***	1.16–1.48
Uric acid (increase of 1.12 mg/dl)‡	4.59***	3.71–5.69
Total protein (increase of 0.39 g/dl)‡	1.16*	1.02–1.32
Hemoglobin A <sub>1c</sub> (increase of 0.64%)‡	0.79*	0.65–0.97
Blood urea nitrogen (increase of 3.50 mg/dl)‡	0.96	0.84–1.10
Hematocrit (increase of 2.8%)‡	1.05	0.92–1.20
White blood cell (increase of 18.0 × 10 <sup>2</sup> /mm <sup>3</sup> )‡	1.17*	1.04–1.31
Drinking alcohol (go/day)	None	1.00
	≤1.9	1.43*
	≥2.0	2.36***
Smoking (cigarettes/day)	None	1.00
	≤29	0.95
	≥30	0.95

\*p<0.05; \*\*p<0.01; \*\*\*p<0.001. †95% confidence interval for hazard ratio. ‡Hazard ratio for an increase of 1 SD; value of 1 SD given in parentheses.

**Table 3.** Multivariate hazard ratios for the incidence of hyperuricemia over a 6.4-yr period on average for selected variables at entry assessed by the Cox Proportional Hazards model

Variables	Model without serum uric acid level		Model with serum uric acid level	
	Hazard ratio	95% confidence interval†	Hazard ratio	95% confidence interval†
Age (increase of 5 yr)	0.86*	0.76–0.96	0.91	0.80–1.02
Body mass index (increase of 2.63 kg/m <sup>2</sup> )‡	1.19**	1.04–1.36	1.16*	1.01–1.34
Diastolic blood pressure (increase of 10.5 mm Hg)‡	1.13	0.99–1.30	1.07	0.93–1.23
Total cholesterol (increase of 34.1 mg/dl)‡	1.05	0.91–1.21	1.05	0.90–1.21
Log triglyceride (increase of 0.545 mg/dl in log <sub>e</sub> )‡	1.17*	1.01–1.35	0.93	0.81–1.08
Uric acid (increase of 1.12 mg/dl)‡	–	–	4.35***	3.49–5.43
Total protein (increase of 0.39 g/dl)‡	1.08	0.94–1.24	0.98	0.85–1.13
Hemoglobin A <sub>1c</sub> (increase of 0.64%)‡	0.84*	0.72–0.98	0.89	0.76–1.05
White blood cell (increase of 18.0 × 10 <sup>2</sup> /mm <sup>3</sup> )‡	1.13*	1.00–1.29	1.13	0.99–1.28
Drinking alcohol (go/day)	None	1.00	1.00	–
	≤1.9	1.47*	1.44*	1.04–1.99
	≥2.0	2.16***	1.86***	1.31–2.63

\*p<0.05; \*\*p<0.01; \*\*\*p<0.001. †95% confidence interval for hazard ratio. ‡Hazard ratio for an increase of 1 SD; value of 1 SD given in parentheses.

impaired glucose tolerance<sup>17, 18, 21, 27</sup>. Furthermore, a few studies have suggested that creatinine is a major determinant of SUA levels<sup>16–18</sup>, but epidemiological evidence regarding SUA is conflicting as to the relation

of SUA levels to total cholesterol, HDL cholesterol, untreated hypertension, and smoking habits<sup>16–21, 24, 25, 27</sup>. In this study, univariate and age-adjusted analyses showed the incidence of hyperuricemia to be significantly

associated with SBP, DBP, the triglyceride level, and total protein level. On the other hand, the HbA<sub>1c</sub> level, when adjusted for age, was significantly inversely associated with the incidence of hyperuricemia. In the model not including the SUA level, the Log triglyceride level was independently associated with the incidence of hyperuricemia. Furthermore, the HbA<sub>1c</sub> level was independently inversely associated with the incidence of hyperuricemia. High HbA<sub>1c</sub> levels may lower SUA levels by enhancing renal excretion of uric acid possibly by inhibiting reabsorption in the proximal tubuli<sup>17, 18, 21, 27</sup>. Our findings therefore highlight the clinical importance of determining hyperuricemia in subjects with other metabolic disorders and vice versa.

Increases in white blood cell levels were significantly associated with increases in the incidence rate of hyperuricemia. The adjusted HR for an increase of 1 SD ( $18.0 \times 10^3/\text{mm}^3$ ) in the white blood cell level achieved marginal statistical significance (1.13, 95% CI: 0.99–1.28,  $p=0.064$ ) even when the SUA level was included as a factor in the model. Characteristically, purine overproduction occurs in myeloid and lymphoid proliferative disorders<sup>28–30</sup>. 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 level plays a causative role in the incidence of hyperuricemia among healthy people.

In this study, age was significantly associated with the incidence of hyperuricemia, even though it had only a weak but significantly negative association with body weight at entry ( $r = -0.127$ ,  $p < 0.001$ ). The negative association of age with the development of hyperuricemia may be partly explained by a relatively high body weight at entry among younger workers. Furthermore, individuals whose USA or blood pressure levels were already elevated when they were younger or who reported having undergone medial treatment for hyperuricemia or hypertension were excluded from this survey. A healthy worker effect may explain the negative association between age and the development of hyperuricemia.

There are several limitations to our study. Identification of incidence cases of increased SUA levels is one problem in conducting longitudinal studies of this common condition. Variability of measurements of SUA in this study (coefficients of variation for SUA of less than 3% throughout the observation period) may make it practicable to establish both normouricemia at the baseline and the subsequent incidence of hyperuricemia in epidemiological studies, but we are fully aware of the limitations implied in our dependence on the annual measurements of SUA to define persons at risk and those developing high levels of SUA.

The second problem concerns the study participants

lost to follow-up during the course of the study. In this study, non-followed up cases did not differ from other cases with respect to age, BMI, SBP, DBP, blood sample data, alcohol intake, or smoking habits at entry. We therefore believe that the influence of non-followed up cases on estimations of the incidence of hyperuricemia was not very strong.

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

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