[ORIGINAL ARTICLE]

Achievement of Target Serum Uric Acid Levels and Factors Associated with Therapeutic Failure among Japanese Men Treated for Hyperuricemia/Gout

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Abstract:

Objective To assess the rate of successfully achieving treatment goals among Japanese men with hyperuricemia/gout and identify factors influencing the success rate.

Methods This cross-sectional study, conducted from January to December 2012, examined the serum uric acid (SUA) levels and clinical characteristics of 2,103 men with hyperuricemia/gout selected from an initial population of 136,770 individuals who participated in a workplace health checkup. The success rates (defined as SUA ≤ 6.0 mg/dL) were calculated, and a multivariate analysis was used to identify factors associated with “therapeutic failure” to achieve target SUA levels.

Results The rate of successfully achieving the target SUA level was 37.5%. The body mass index (BMI) was significantly associated with therapeutic failure [$25.0 \leq$ Category (C) $2 < 27.5$, adjusted odds ratio (AOR) = 1.35; $27.5 \leq$ C3 < 30.0 , AOR=1.69; C4 ≥ 30.0 , AOR=1.94; relative to C1 < 25.0]. A significant positive association was also observed between waist circumference (WC) and therapeutic failure ($85 \leq$ C2 < 90 , OR=1.29; $90 \leq$ C3 < 95 , OR=1.41; $95 \leq$ C4, OR=2.28; relative to C1 < 85.0 cm). Those with higher BMI/WC measurements were significantly more likely to have higher SUA levels than those with lower such measurements. The ongoing intake of dyslipidemia medication was identified as a protective factor against therapeutic failure.

Discussion Our findings suggest a possible association between obesity and therapeutic failure, underscoring the importance of maintaining lipid profiles as part of managing SUA levels. Better management of both obesity and dyslipidemia may prevent future cardiovascular disorders by ensuring healthier SUA levels.

Key words: uric acid, obesity, achievement rate, lifestyle-related disorder, prevention, epidemiology

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Introduction

Hyperuricemia is a major risk factor for cardiovascular disease (CVD), chronic kidney disease (CKD), gout, and metabolic syndrome (1-4), and some experimental studies have indicated a modulatory or causal role of hyperuricemia in these disorders (5-7). Primary hospitalization rates for gout have increased substantially for the past nearly two decades in the United States, while those for rheumatoid arthritis have declined (8). The prevalence of hyperuricemia is

estimated to be approximately 25% among Japanese adult men, with the number of patients with gout in 2004 having increased by 2.1-fold compared to 1995 and by 3.4-fold compared to 1986 (9). According to the guidelines of The Japanese Society of Gout and Nucleic Acid Metabolism, hyperuricemia is defined as a serum uric acid (SUA) level ≥ 7.0 mg/dL. Based on several previous empirical studies (9-11), it is recommended that the SUA levels be kept at ≤ 6.0 mg/dL among patients with a high risk of gout in order to ensure primary or secondary prevention. In fact, several intervention studies have demonstrated that SUA-lowering

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Figure 1. Patient registration and flowchart of the study.

agents reduce the incidence and recurrence of gout (12). Thus, these treatment guidelines suggest that the management of hyperuricemia/gout is an important way to help prevent these disorders. However, limited evidence is available on the actual status of SUA management in Japan.

The present study therefore aimed to assess the rate of successfully achieving treatment goals and explore factors associated with therapeutic failure among Japanese men with hyperuricemia/gout.

Materials and Methods

This was a cross-sectional study screening 136,770 Japanese adults [≥ 65 years of age; 4,593 (3.4%)] who participated in a workplace health checkup conducted by the Tokyo Health Service Association from January to December 2012 in Tokyo, Japan. Of the 2,594 subjects deemed to have hyperuricemia/gout, 478 were excluded due to missing data on SUA, and 13 women were additionally excluded because they comprised a proportion that was too small for an analysis. Ultimately, 2,103 men were included in the present study [≥ 65 years of age; 195 (9.3%)] (Fig. 1).

Variables

The height, weight, body mass index (BMI), and waist circumference (WC) were measured with participants in the standing position. The BMI was calculated by dividing the body weight (kg) by the height squared (m^2). The mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated from the means of two upper arm blood pressure measurements taken from participants who had been seated for at least five minutes. Serum levels of total cholesterol (mg/dL; TC), high-density lipoprotein cholesterol (mg/dL; HDL-C), low-density lipoprotein cholesterol (mg/dL; LDL-C), and triglycerides (mg/dL; TG) were also measured. LDL-C was estimated using the Friedewald equation ($\text{TC} - \text{HDL-C} - \text{TG}/5$) (13). Hemoglobin A1c (HbA1c) levels were determined by high-performance liquid chromatography using an automated analyzer. HbA1c [Japanese Diabetes Society (JDS; %)] values were converted to National Glycohemoglobin Standardization Program (NGSP) equivalent values using the following formula: $\text{HbA1c (NGSP) (\%)} = 1.02 \times \text{HbA1c (JDS) (\%)} + 0.25\%$ (14). SUA

was measured with the uricase-peroxidase method. The estimated glomerular filtration rate (eGFR) was calculated using the Japanese GFR equation: $\text{eGFR (mL/min/1.73 m}^2\text{)} = 194 \times \text{Cr}^{-1.094} \times \text{age}^{-0.287}$.

Participants were asked to complete a self-administered questionnaire that addressed healthy lifestyle characteristics based on Breslow's seven health practices (15). These characteristics can be used to assess lifestyle health, and strong associations have been found between healthy lifestyle items and successful blood pressure control among patients with hypertension (16). Healthy lifestyle items in the questionnaire included non-daily alcohol consumption, non-smoker status, exercise frequency of two or more times per week, a BMI of 18.5–24.9 kg/m^2 , adequate sleep duration, daily breakfast consumption, and no snacking between meals (15, 16).

From the self-administered questionnaire, we also collected information on a present medical history of comorbidities, such as hyperuricemia/gout, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, cerebrovascular disease, and kidney disease. If participants acknowledged having these comorbidities, we registered them as having a present medical history of these comorbidities.

Statistical analyses

The results are presented as mean $\pm$ standard deviation (SD) for continuous variables or prevalence (%) for categorical variables. The BMI (kg/m^2) and WC (cm) were divided into the following categories: BMI (kg/m^2) = C1 < 25.0, $25.0 \leq \text{C2} < 27.5$, $27.5 \leq \text{C3} < 30.0$, $30.0 \leq \text{C4}$; WC (cm) = C1 < 85, $85 \leq \text{C2} < 90$, $90 \leq \text{C3} < 95$, $95 \leq \text{C4}$. The target SUA level was defined as ≤ 6.0 mg/dL (356.9 $\mu\text{mol/L}$) based on the treatment guidelines. The “controlled group” and “uncontrolled group” comprised those with SUA levels ≤ 6.0 and > 6.0 mg/dL, respectively (9). Factors associated with therapeutic failure in achieving target SUA levels were identified using odds ratios (ORs) and 95% confidence intervals (CIs) for each item, with a univariate logistic regression analysis and two multivariate models providing adjusted ORs (AORs) and 95% CIs. Model 1 was adjusted for age (years), BMI, hypertension medication (yes), diabetic medication (yes), dyslipidemia medication (yes), alcohol consumption (non-daily drinker), smoking (non-smoker), and eGFR (mL/min/1.73 m^2). Model 2 was adjusted for age (years), WC, hypertension medication (yes), diabetic medication (yes), dyslipidemia medication (yes), alcohol consumption (non-daily drinker), smoking (non-smoker), and eGFR (mL/min/1.73 m^2).

The SUA levels were compared between C1 and other quartiles with Dunnett's method. Trends in p values were estimated using the Jonckheere-Terpstra test for continuous variables. For the two-tailed Student's *t*-test, $p < 0.05$ was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences, version 22 (SPSS, Chicago, USA).

The research protocol was reviewed and approved by the

Table 1. Participant Characteristics (n=2,103).

	Mean (SD) or N (%)		
	Uric acid (mg/dL)		
	≤ 6.0 (n=788)	>6.0 (n=1,315)	
Age (years)	54.2 (9.5)	53.1 (9.5)	**
Anthropometric measurements			
Body mass index (kg/m²)	25.1 (3.3)	25.8 (3.7)	**
Waist circumference (cm)	88.5 (8.4)	90.3 (9.4)	**
Healthy lifestyle characteristics			
Alcohol consumption (non-daily drinker)	443 (56.2)	752 (57.2)	
Smoking behavior (non-smoker)	548 (76.9)	920 (77.2)	
Exercise frequency (2 times or more per week)	360 (50.5)	597 (50.1)	
Body mass index (18.5-24.9)	428 (54.3)	598 (45.5)	**
Adequate sleep duration (yes)	474 (66.6)	755 (63.5)	
Breakfast (every morning)	602 (84.6)	1,001 (84.1)	
Snack between meals (no)	649 (91.0)	1,074 (90.2)	
Proportion of participants with 6 or 7 total number of healthy lifestyle items	208 (29.3)	300 (25.3)	
Hypertensive medication (yes)	313 (43.9)	525 (44.0)	
Systolic blood pressure (mmHg)	128.7 (17.2)	129.9 (17.6)	
Diastolic blood pressure (mmHg)	80.6 (10.7)	81.8 (11.2)	*
Diabetic medication (yes)	49 (6.9)	79 (6.6)	
Hemoglobin A1c (%)	5.4 (0.7)	5.4 (0.7)	
Dyslipidemia medication (yes)	223 (31.3)	322 (27.0)	*
Total cholesterol (mg/dL)	198.9 (32.1)	204.5 (34.3)	**
High density cholesterol (mg/dL)	56.0 (13.5)	54.1 (13.7)	**
Low density cholesterol (mg/dL)	114.2 (29.9)	117.8 (29.6)	**
Triglyceride (mg/dL)	168.8 (149.6)	175.5 (145.7)	
Uric acid (mg/dL)	5.2 (0.7)	7.2 (0.9)	**
Organ damage/cardiovascular disease			
Heart	38 (4.8)	60 (4.6)	
Brain	11 (1.4)	14 (1.1)	
Kidney	2 (0.3)	12 (0.9)	
eGFR (mL/min/1.73 m²)	73.5 (15.1)	70.2 (15.3)	**

N: number, SD: standard deviation, eGFR: estimated glomerular filtration rate, *p<0.05, **p<0.01

Ethics Committee of the Tokyo Health Service Association, and written informed consent was obtained from all participants.

Results

The proportion of participants in the controlled group [SUA level ≤6.0 mg/dL (356.9 μmol/L)] was 37.5%, which represented the rate of successfully achieving the treatment goal. The mean ages (SD) of the controlled and uncontrolled groups were 54.2 (9.5) and 53.1 (9.5) years, respectively (Table 1). The uncontrolled group had significantly higher mean values for the BMI, WC, DPB, TC, and LDL-C and significantly lower values for the HDL-C and eGFR than the controlled group. The proportion of those taking dyslipidemia medication was significantly higher in the controlled group than in the uncontrolled group.

A multivariate logistic regression analysis revealed the factors associated with therapeutic failure of hyperuricemia/gout (Table 2). In Model 1, C2, C3, and C4 of the BMI were significantly positive associated with therapeutic failure

compared to C1 (C2, AOR=1.35, 95% CI=1.03-1.76; C3, AOR=1.69, 95% CI=1.12-2.42; C4, AOR=1.94, 95% CI=1.26-2.98). In Model 2, C3 and C4 of the WC were significantly positive associated with therapeutic failure compared to C1 (C2, AOR=1.29, 95% CI=0.95-1.75; C3, AOR=1.41, 95% CI=1.01-1.97; C4, AOR=2.28, 95% CI=1.63-3.18). In addition, taking dyslipidemia medication was significantly negative associated with therapeutic failure in both models (AOR=0.74 and 95% CI=0.57-0.95 in Model 1, AOR=0.71 and 95% CI=0.55-0.92 in Model 2). Those in the higher BMI/WC categories were significantly more likely to have higher SUA levels than those in lower such categories (Fig. 2, 3).

Discussion

Our cross-sectional study revealed a low achievement rate of 37.5% for target SUA levels among Japanese men with hyperuricemia/gout. In addition, significant associations between therapeutic failure and BMI/WC categories were observed after adjusting for confounding factors. Increased

Table 2. Factors Associated with Therapeutic Failure among Men (logistic Regression Analysis) (n=2,103).

	Mean (SD) or N (%)	Univariate			Multivariate					
		OR	95% CI	p	Model 1			Model 2		
					AOR	95% CI	p	AOR	95% CI	p
Body mass index (kg/m ²)										
C1<25.0	1,040 (49.5)		-			-			-	
25.0≤ C2<27.5	541 (25.7)	1.26	1.02-1.56	*	1.35	1.03-1.76	**		-	
27.5≤ C3<30.0	299 (10.6)	1.49	1.14-1.96	**	1.69	1.12-2.42	*		-	
30.0≤ C4	222 (10.6)	1.89	1.37-2.60	**	1.94	1.26-2.98	**		-	
Waist circumference (cm)										
C1<85.0	667 (32.8)									
85.0≤ C2<90.0	487 (23.9)	1.21	0.95-1.53	*				1.29	0.95-1.75	
90.0≤ C3<95.0	374 (18.4)	1.24	0.96-1.61	*				1.41	1.01-1.97	*
95.0≤ C4	508 (25.0)	1.77	1.38-2.26	**				2.28	1.63-3.18	**
Age (years)	53.5 (9.5)	0.99	0.98-0.99	*	0.98	0.97-0.99	**	0.97	0.96-0.99	**
Hypertensive medication (yes)	838 (39.8)	1.01	0.93-1.21		1.03	0.81-1.32		0.99	0.77-1.27	
Diabetic medication (yes)	128 (6.1)	0.96	0.66-1.39		0.92	0.59-1.43		0.90	0.57-1.41	
Dyslipidemia medication (yes)	545 (25.9)	0.81	0.66-0.99	*	0.74	0.57-0.95	*	0.71	0.55-0.92	**
Alcohol consumption (non-daily drinker)	1,195 (56.8)	1.04	0.87-1.24		0.80	0.64-1.01		0.81	0.64-1.04	
Smoking behavior (non-smoker)	1,468 (69.8)	1.02	0.82-1.27		0.99	0.76-1.31		1.07	0.81-1.41	
eGFR (mL/min/1.73 m ²)	71.4 (15.3)	0.99	0.98-0.99	**	0.98	0.97-0.99	**	0.98	0.97-0.99	**

N: number, SD: standard deviation, OR: odds ratio, AOR: adjusted odds ratio, CI: confidence interval, eGFR: estimated glomerular filtration rate

*p<0.05, **p<0.01

Model 1 was adjusted for body mass index categories, age (years), hypertension medication (yes), diabetic medication (yes), dyslipidemia medication (yes), alcohol consumption (non-daily drinker), smoking (non-smoker), and eGFR (mL/min/1.73 m²).

Model 2 was adjusted for waist circumference categories, age (years), hypertension medication (yes), diabetic medication (yes), dyslipidemia medication (yes), alcohol consumption (non-daily drinker), smoking (non-smoker), and eGFR (mL/min/1.73 m²).

Figure 2. Relationship between the body mass index categories and the serum uric acid levels among men with hyperuricemia/gout.

BMI/WC categories showed a positive linear association with the SUA level. However, a medical history of dyslipidemia was a protective factor against therapeutic failure. To our knowledge, few studies have investigated the rates of success in treating hyperuricemia/gout or factors associated with therapeutic failures in the Japanese population; the present study therefore offers novel insight on this matter.

We observed low rates of achieving treatment goals among men with hyperuricemia/gout. Several experimental

intervention studies have reported the efficacy of hyperuricemia medication (17, 18). One clinical trial, which was a randomized multi-center double-blind study conducted in Japan [mean age (SD): 51.4 (8.2) years], found that SUA levels ≤ 6.0 mg/dL (356.9 μmol/L) were achieved in 76.9% of patients after they had been treated with 129 mg topiroxostat (continuation rate: 89.0%) (17). In another 12-week, multi-center, open-label, uncontrolled study in Japan [mean age (SD): 47.9 (11.1) years], the SUA levels at baseline and af-

Figure 3. Relationship between the waist circumference categories and serum uric acid levels among men with hyperuricemia/gout.

ter administration of the antihyperuricemic fuxostat were reportedly 9.34 ± 1.48 and 5.59 ± 1.17 mg/dL, respectively, while those among normal excretors were 8.59 ± 1.24 and 5.41 ± 1.35 mg/dL, respectively, and those among underexcretors were 8.29 ± 1.01 and 5.11 ± 1.71 mg/dL, respectively (18). Although these studies demonstrated high rates of achievement under several criteria, there are some discrepancies between their findings and ours. One possible explanation for this may be the awareness of target goals among physicians. A Japanese study conducted a questionnaire survey of 595 Japanese board-certified nephrologists for their criteria with regard to SUA levels in order to start urate-lowering therapy and identify a target level for chronic kidney disease with hyperuricemia (19). The survey reported respective start and target SUA levels of 8.2 ± 0.9 mg/dL and 6.9 ± 0.9 mg/dL, 8.4 ± 0.9 mg/dL and 7.0 ± 1.0 mg/dL, 8.6 ± 1.0 mg/dL and 7.3 ± 1.1 mg/dL, and 9.1 ± 1.2 mg/dL and 7.8 ± 1.3 mg/dL at stages 3, 4, 4D, and 5D, respectively, revealing a discrepancy between the target levels recommended by treatment guidelines and those recommended by physicians. Therefore, awareness among physicians must be improved in order to better manage SUA levels in line with treatment guidelines.

One other reason that may explain the discrepancy in our findings and others' is medication adherence among patients. A meta-analysis of data from 376,162 patients evaluated by 20 cardiovascular disease studies estimated an adherence rate of 57% across all studies (95% CI, 50-64) after a median of 24 months (20). Although we did not assess the medication adherence within our study population, it may have been similar to that of previous studies and lower than that of experimental clinical trials. Thus, improved medication adherence may also be necessary in actual clinical settings in order to achieve better management of SUA levels.

Our study found that the BMI and WC were significantly associated with therapeutic failure among participants with hyperuricemia/gout. Previous reports have identified a positive association between obesity and uric acid levels (21-23). An epidemiological survey of 699 diabetic patients who had

undergone an abdominal computed tomography assessment of the visceral fat area reported that a visceral fat area >143 cm² was a significant independent predictor of hyperuricemia (OR 2.33, 95% CI, 1.21-4.50, $p=0.012$), as opposed to a visceral fat area <93 cm², after adjusting for confounders (22). A large cross-sectional population study revealed in its SUA analysis that the chronic intake of sugar-sweetened beverages was associated with an increased SUA level in the high-BMI group but not in the low-BMI group (p difference = 3.6×10^{-3}); the chronic intake of sugar-sweetened beverages was also found to be associated with gout in the high-BMI group but not in the low-BMI group (p difference = 0.012) (23). Several other interventional studies have revealed the impact of weight loss for improving hyperuricemia/gout (24, 25). The Multiple Risk Factor Intervention Trial, which analyzed 12,379 men with high cardiovascular risk profiles, reported that relative to those with no weight change (-0.9 to 0.9 kg), the multivariate ORs of achieving normo-SUA levels after weight loss of 1-4.9 kg, 5-9.9 kg, and ≥ 10 kg were 1.43 (95% CI: 1.33, 1.54), 2.17 (1.95, 2.40), and 3.90 (3.31, 4.61), respectively, while the corresponding changes in SUA levels were -0.12 , -0.31 , and -0.62 mg/dL (-7 , -19 , and -37 μ mol/L) (25). Thus, lifestyle modification to maintain an ideal body weight may be an option for treating hyperuricemia/gout.

Interestingly, our results indicate that having a medical history of taking dyslipidemia medication was a protective factor against therapeutic failure to meet SAU treatment goals. While this result seems contradictory, one potential explanation may be the association between SUA levels and lipid profiles (26, 27). A cohort study of 4,706 Chinese residents reported that per-unit increases in the BMI, BP, TG, and LDL-C levels were associated with 1.103-, 1.016-, 1.173-, and 1.200-fold higher odds of the presence of hyperuricemia, and per-unit increases in HDL-C and FBG levels were associated with 0.616- and 0.900-fold lower odds of the presence of hyperuricemia, respectively (26). A retrospective 5-year cohort study of 6,476 healthy Japanese

adults reported that a high baseline SUA was an independent risk factor for developing high LDL cholesterol in both men (OR: 1.159 per 1-mg/dL increase, 95% CI: 1.009-1.331) and women (OR: 1.215, 95% CI: 1.061-1.390). Increased SUA levels for longer than 5 years also represented an independent risk factor for developing high LDL cholesterol levels and hypertriglyceridemia but not for developing low levels of HDL-C (27). In our study, the controlled group had lower LDL-C levels and higher HDL-C levels than the uncontrolled group. In addition, the LDL-C levels were significantly lower and the HDL-C levels higher in those taking dyslipidemia medication than in those who were not [LDL-C: 112.1 (30.5) vs. 117.7 (29.2) mg/dL, HDL-C: 55.5 (14.1) vs. 52.7 (11.8) mg/dL (data not shown)]. It is possible that better management by lowering lipid levels may help maintain SUA levels. Accordingly, comprehensive management, including that of lipid profiles, may be needed to ensure better treatment of hyperuricemia/gout.

Several limitations associated with the present study warrant mention. First, selection bias may have occurred, as participants comprised only those who underwent workplace medical checkups in Tokyo, Japan. As such, these participants may be inherently more aware of their health behaviors than residents in rural areas. Further analyses that include data from a more diverse cohort are needed. Second, some key data on items such as detailed information regarding medication, medication dosage, and medication adherence were not collected. Third, this study had a cross-sectional design, so causal relationships between elevated SUA levels and obesity could not be evaluated. Further analyses of follow-up survey data will be needed to address this issue.

In conclusion, our large-scale cross-sectional study revealed low rates of achieving the target SUA level, and significant associations between therapeutic failure and the BMI/WC categories were observed after adjusting for confounders among participants with hyperuricemia/gout. We also found that the BMI/WC categories were positively associated with SUA levels, while a medical history of dyslipidemia was a protective factor against therapeutic failure. Collectively, these findings suggest a possible association between the rate of achieving target SUA levels and obesity while underscoring the importance of maintaining healthy lipid profiles as a way to manage uric acid levels. Better management of obesity in addition to that of dyslipidemia may help prevent the future development of cardiovascular disorders by maintaining healthy SUA levels.

The authors state that they have no Conflict of Interest (COI).

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to this work.

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