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Serum Uric Acid Level Has Stronger Correlations with Metabolic Syndrome-Related Markers in Women than in Men in a Japanese Health Check-Up Population

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Abstract

Background A serum uric acid (UA) level of 7.0 mg/dL has been used as the criterion for hyperuricemia in Japan regardless of gender, despite higher serum UA levels in men than in women. Serum UA has been identified as a predictive biomarker for metabolic syndrome (MetS); however, the gender differences in the association between UA levels and MetS-related conditions in a Japanese population have not been completely assessed. ***Objective*** To examine gender and age differences in the associations between serum UA levels and other biomarkers within a health-screened Japanese population and to evaluate the usefulness of serum UA as a predictor of MetS between the two genders. ***Methods*** A cross-sectional study of healthy individuals in Japan (16,391 men; 16,656 women) was conducted. Associations between UA and several biomarkers were analyzed for each gender type and for age- and serum UA level-stratified groups. Logistic regression was used to analyze the association of age and serum UA levels with MetS-related conditions. Receiver operating characteristic (ROC) curve analysis was performed to identify the UA cut-off value for predicting the risk of the MetS-related conditions. ***Results*** Serum UA levels in women had stronger correlations with MetS-related biomarkers than in men. After adjusting for age, the odds ratios for a 1-mg/dL serum UA increase for diabetes mellitus and dyslipidemia in women were 1.13 (95% confidence interval, 1.04 - 1.23) and 1.30 (1.25 - 1.34), respectively. In ROC analysis, women had significantly higher area under the curve (AUC) values for MetS prediction than men. ***Conclusion*** An elevated serum UA level has a higher predictive ability for the risk of MetS-related conditions in Japanese women than in men. The optimal serum UA cut-off value for MetS in women was suggested to be approximately 5 mg/dL, re-

markably lower than that in men.

Keywords

Urate, Metabolic Syndrome, Gender Difference, Health Check

1. Introduction

Elevated levels of uric acid (UA) in the circulation, or hyperuricemia, have been shown to be associated with metabolic syndrome (MetS) and MetS-related diseases such as diabetes mellitus (DM) and coronary artery disease. MetS is defined as a condition of excessive waist circumference along with one or more of the following symptoms: lipid abnormality, hypertension, and glucose intolerance [1]. Excessive production of UA and decreased renal excretion have been implicated in the association between MetS and hyperuricemia [2] [3]. Recent studies in genetic epidemiology have also shown that although UA likely plays a minor causative role in the pathophysiology of diseases such as DM, cardiovascular disease (CVD), and chronic kidney disease (CKD), it can serve as a biomarker with predictive value for these diseases [4] [5]. A recent noteworthy finding is that, despite the low levels of serum UA in women, several studies have demonstrated a stronger association between serum UA levels and the onset of MetS in women than in men [6] [7] [8].

In Japan, the current criteria for hyperuricemia refer to a serum UA level over 7.0 mg/dL in both adult men and women [9]. However, sex hormones have a profound influence on UA metabolism [10]. Indeed, several studies have shown that serum UA levels are generally lower in women relative to men; however, strong associations between serum UA and other parameters in women have also been reported [6] [7] [8]. Few studies have compared serum UA levels suitable for risk prediction of MetS-related diseases in men and women. It is also unclear how the UA-MetS relationship is influenced by age and menopause in females who participate in health screenings in Japan.

In this study, we used a dataset obtained from the Yuport Medical Checkup Center study to examine gender and age differences of serum UA levels in a Japanese population. We also aimed to derive a cut-off value for serum UA levels to be used as a gender-specific predictor of MetS.

2. Methods

A cross-sectional study was performed using a dataset obtained from the health screening program conducted in 1998 to 2006 in Tokyo and the surrounding area in Japan by the Yuport Medical Checkup Center. The sample consisted of middle-aged and older individuals drawn from the Japanese general population (16,391 men and 16,656 women) [11] [12]. These subjects corresponded to all the individuals with all the parameters described in this section and in **Table 1** available, and therefore no exclusion criteria were applied. This study was ap-

proved by the Ethics Committee of Teikyo University School of Medicine (No. 15-205-2).

Body mass index (BMI) was calculated as an individual's body weight (in kilograms) divided by their height squared (in meters). Systolic blood pressure (SBP), and diastolic blood pressure (DBP) were all measured using standard procedures. Fasting serum triglycerides (TGs), serum HDL-cholesterol, fasting plasma glucose (FPG, ≥8 hours after the last caloric intake), serum creatinine, serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), and serum UA values were all measured using the same methods described in ref [12]. For serum low-density lipoprotein (LDL)-cholesterol, the estimate based on the Friedewald equation was used [11].

Table 1. Anthropometric and biochemical participant characteristics.

	Men (16,391)	Women (16,656)
Age (years)	51.2 ± 13.2	52.4 ± 13.0
Uric acid (mg/dL)	6.1 ± 1.3	4.5 ± 1.0
Body mass index (kg/m^2)	23.6 ± 3.0	22.1 ± 3.1
Systolic blood pressure (mmHg)	126.7 ± 17.5	120.7 ± 18.5
Diastolic blood pressure (mmHg)	77.4 ± 11.0	72.6 ± 11.0
Leukocytes (cells/μL)	60.7 ± 16.8	53.9 ± 16.3
Platelets (cells/μL)	22.8 ± 5.0	23.4 ± 5.2
Fasting plasma glucose (mg/dL)	102.2 ± 21.4	94.4 ± 15.9
Hemoglobin A1c (%)	5.4 ± 0.9	5.3 ± 0.6
C-reactive protein (mg/dL)	0.14 ± 0.4	1.00 ± 0.3
Albumin (g/dL)	4.5 ± 0.3	4.4 ± 0.2
Total bilirubin (mg/dL)	0.8 ± 0.3	0.7 ± 0.3
Aspartate aminotransferase U/L)	22 (18 - 27)	19 (17 - 20)
Alanine aminotransferase (U/L)	22 (16 - 32)	15 (12 - 20)
Alkaline phosphatase (U/L)	163.3 ± 57.7	163.4 ± 63.4
***γ*-Glutamyl transpeptidase (U/L)**	28 (17 - 49)	14 (10 - 22)
Lactate dehydrogenase (U/L)	118.5 ± 32.1	254.2 ± 84.6
Triglycerides (mg/dL)	110.0 (77 - 160)	78.0 (57 - 109)
Total cholesterol (mg/dL)	198.0 ± 34.0	206.6 ± 36.4
HDL cholesterol (mg/dL)	52.3 ± 13.3	62.6 ± 14.2
LDL cholesterol (mg/dL)	120.0 ± 30.7	125.9 ± 32.9
Creatinine (mg/dL)	0.8 ± 0.2	0.6 ± 0.1
Blood urea nitrogen (mg/dL)	14.9 ± 3.6	14.1 ±3.6
eGFR (mL/min/1.73m^2)	81.2 ± 15.8	82.9 ± 16.6

Values are represented as the mean ± SD, or median (25-75th percentile range). HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate. Except for alkaline phosphatase, all measurements had significant gender differences with $P < 0.001$.

The estimated glomerular filtration rate (eGFR) was calculated using the formula proposed by the Modification of Diet in Renal Disease study and modified for the Japanese population. The equation used was: 194 × (serum creatinine)$^{-1.094}$ × (age)$^{-0.287}$, with the result further multiplied by 0.739 for women [13].

As waist circumference data were not available in this study, instead of the criteria for MetS [1], the "MetS-like state" was used, which was defined by the presence of two or more of the following conditions: TG/HDL-based dyslipidemia (TG ≥ 150 mg/dL or HDL-cholesterol < 40 mg/dL), high blood pressure (SBP ≥ 130 mmHg or DBP ≥ 85 mmHg), or hyperglycemia (FPG ≥ 110 mg/dL). Dyslipidemia was defined as LDL-cholesterol ≥ 140 mg/dL, HDL-cholesterol < 40 mg/dL, or TG ≥ 150 mg/dL. DM was defined as FPG ≥ 126 mg/dL, random plasma glucose ≥ 200 mg/dL, or HbA1c (National Glycohemoglobin Standardization Program) ≥ 6.5%.

With these criteria, multivariate logistic regression analysis was performed to examine the relationship between age, serum UA, and the presence of DM, dyslipidemia, and the MetS-like state.

In our receiver operating characteristic (ROC) analyses, area under the ROC curves (AUCs) were used to assess model performance. Optimal cut-off values were inferred using Youden's index, defined as J = sensitivity + specificity − 1 ($0 \le J \le 1$) and derived from the ROC curves [14]. All statistical analyses were carried out using SPSS software (SPSS Inc., Chicago, IL, USA).

3. Results

From the health screening program dataset, the data of all individuals were used without exclusion criteria, which consisted of 16,391 men and 16,656 women. The demographic and clinical characteristics of the study participants are presented in **Table 1**. The mean age (±SD) of the participants was 50.8 (±13.1) years for men and 52.0 (±13.0) years for women. Thus, the population we used was similar to that of recent Korean [15] and Japanese [16] studies, although the female population in our study was slightly older than the population in the study by Tani *et al.* (mean age = 48.6 years) [16]. With the exception of alkaline phosphatase, for all parameters there were significant differences between men and women. Similar to the results of earlier studies on Japanese populations [16] [17], many biomarkers, including serum UA, BMI, SBP, DBP, FPG, HbA1c, and TG, were significantly higher in men than in women. Conversely, total cholesterol, HDL-cholesterol, and LDL-cholesterol values were significantly higher in women than in men.

In the population analyzed, 1269 (8.4%) men and 536 (3.3%) women were diagnosed with DM. Furthermore, 5765 (35.1%) men and 1917 (11.8%) women were diagnosed with dyslipidemia, while 5580 (34.0%) men and 2043 (12.3%) women were diagnosed with the MetS-like state. In total, 24.0% of the men and 1.7% of the women had serum UA levels ≥ 7.0 mg/dL.

Analysis of the serum UA values across age-stratified groups showed higher

serum UA levels in men across all ages (Figure 1). In the groups aged 42 years and above, the serum UA level linearly increased with age in women, but the opposite was seen in some age groups in men. Given that the median age of menopause of Japanese women is 50.5 [18], the result suggested that serum UA linearly increased with age in women in their postmenopausal period.

We then analyzed the Spearman's correlation coefficients between serum UA and a wider set of biomarkers (Table 2). For most markers, including blood pressure, lipid markers, BMI, and glucose, the correlation coefficient fell within the range of 0.1 - 0.3, implying a weak correlation. Nonetheless, except for HbA1c, total bilirubin and lactate dehydrogenase in men, all biomarkers analyzed showed significant correlations ($P < 0.001$). Except for albumin, γ-glutamyl transpeptidase and HDL-cholesterol, all markers showed more pronounced correlations in women relative to men. Notably, the correlations of serum UA level with FPG and HbA1c showed between-gender discordance, with a negative and positive coefficient for men and women, respectively.

Table 2. Spearman correlation coefficients between serum UA level and various biomarkers.

	Men (16,391)	Women (16,656)
Body mass index (kg/m^2)	0.254	0.279
Systolic blood pressure (mmHg)	0.141	0.201
Diastolic blood pressure (mmHg)	0.147	0.181
Leukocytes (cells/μL)	0.096	0.144
Platelets (cells/μL)	0.037	0.064
Fasting plasma glucose (mg/dL)	0.059	0.184
Hemoglobin A1c (%)	0.003	0.191
C-reactive protein (mg/dL)	0.095	0.186
Albumin (g/dL)	0.146	0.109
Total bilirubin (mg/dL)	−0.008	−0.023
Aspartate aminotransferase (U/L)	0.206	0.219
Alanine aminotransferase (U/L)	0.223	0.233
Alkaline phosphatase (U/L)	−0.033	0.119
γ-Glutamyl transpeptidase (U/L)	0.235	0.184
Lactate dehydrogenase (U/L)	0.004	0.108
Triglycerides (mg/dL)	0.257	0.277
Total cholesterol (mg/dL)	0.115	0.200
HDL cholesterol (mg/dL)	−0.127	−0.125
LDL cholesterol (mg/dL)	0.045	0.190
Creatinine (mg/dL)	0.272	0.276
Blood urea nitrogen (mg/dL)	0.041	0.191
eGFR (mL/min/1.73m^2)	−0.213	−0.334

All correlations except for those with an underline showed significance ($P < 0.001$).

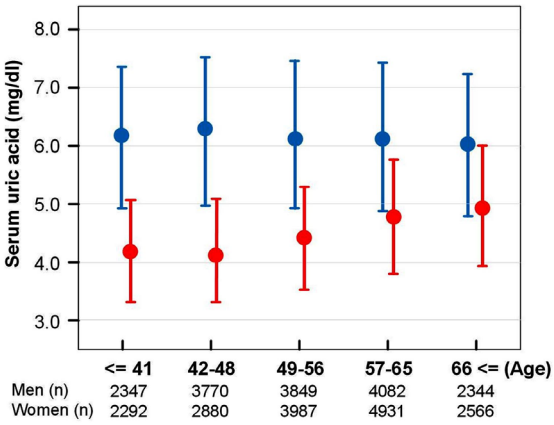

Figure 1. Mean serum UA levels by age-stratified subgroup. The data for men (blue circles) and women (red circles) are presented along with SD values indicated by error bars. The number of participants belonging to each age group is shown below the plot.

To gain further insight into the relationships between serum UA and MetS-related biomarkers, the participants were classified into five groups according to their serum UA level as described in the legend for **Figure 2**. The mean biomarker value for each group was plotted for several biomarkers. For both men and women, many of the biomarkers, including BMI, SBP, TG, BUN, and creatinine, showed increasingly higher values with increasing UA levels, whereas eGFR and HDL-cholesterol showed lower values (**Figure 2**).

As we predicted from the correlation coefficients (**Table 2**), serum UA level showed stronger associations with many biomarkers in women relative to men, though γ-GT and ALT showed rather modest associations in woman relative to men (**Figure 2**). Gender differences were seen for several serum UA-biomarker relationships, including lipid markers and blood pressure. For example, the difference in BMI between the high-UA and low-UA group was more pronounced in women than in men. Between-gender discordance was seen for HbA1c and FPG, with a positive association in women and a negative association in men. CRP exhibited a trend similar to the glucose-related markers. Intriguingly, BUN also showed a remarkable gender-difference; women showed a positive association while men showed little difference between the UA-stratified groups. Although creatinine showed a rather modest gender difference, the difference of eGFR was starker; women displayed a high sensitivity to serum UA level, whereas men showed only a modest degree of such dependency.

To better characterize the age- and sex-dependency of the associations between serum UA and biomarkers, we stratified the participants into three age groups and repeated the analysis. The results are shown in **Figure 3** for BMI, HbA1c, and BUN as the biomarkers that showed pronounced between-gender differences.

Broadly, the aged group showed a more pronounced association between serum UA and BMI in the men (**Figure 3**, *top*, *left*), while a clearer association was seen in the younger group in the women. For HbA1c in men, the negative UA-HbA1c correlation was more evident in the aged group (**Figure 3**, *top*, *middle*). For

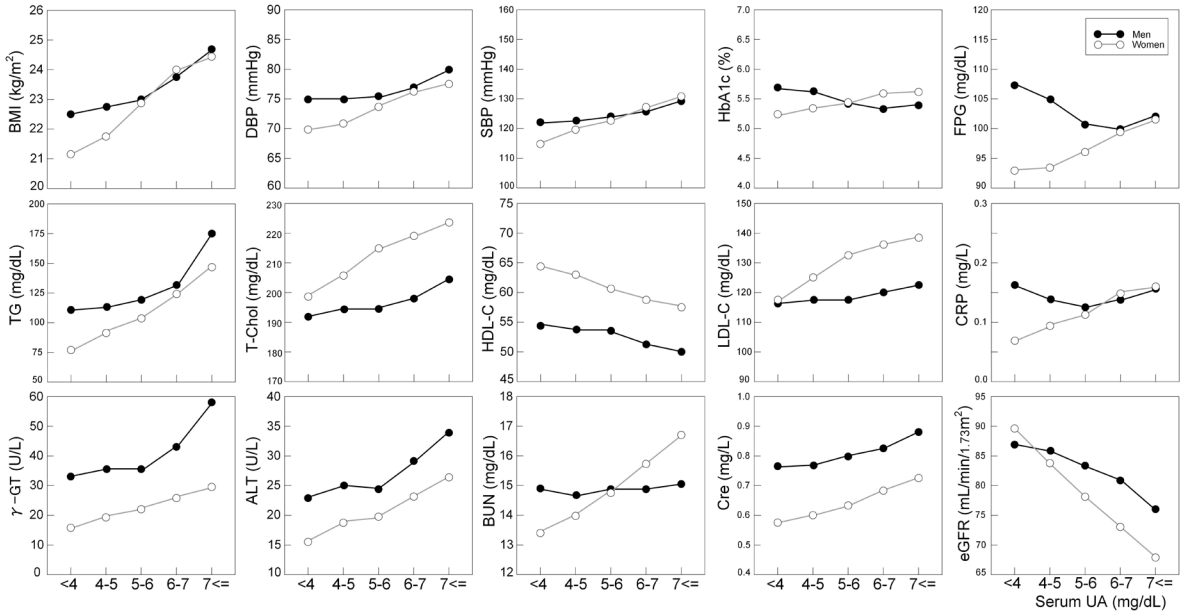

Figure 2. The relationship between serum UA and several biomarkers. The x-axis represents five groups stratified according to UA level in mg/dL. The number of participants in each UA-stratified group was: "<4", (Men 694, Women 4814); "4 - 5", (2080, 6801); "5 - 6", (4807, 3688); "6 - 7", (4873, 1063); "≥7", (3937, 290). SUA, serum uric acid; T-Chol, total cholesterol; HDL-C, HDL-cholesterol, LDL-C, LDL-cholesterol; CRP, C-reactive protein; γ-GT, gamma-glutamyl transpeptidase; Cre, creatinine.

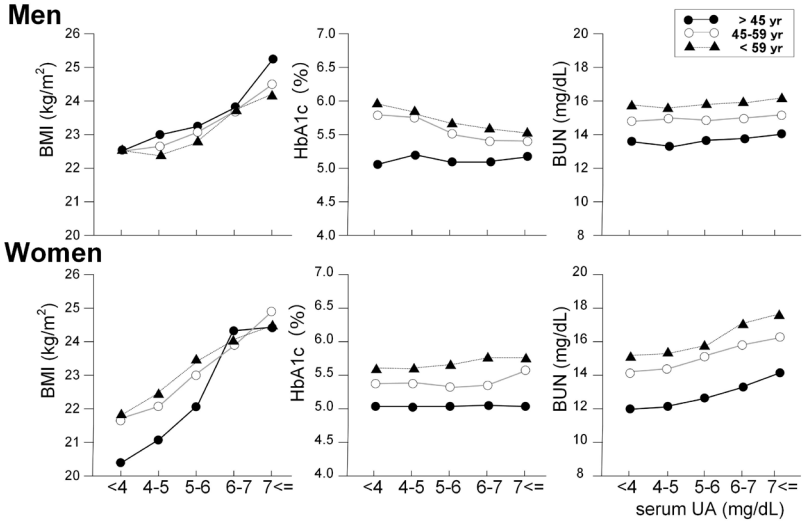

Figure 3. Relationship between serum UA and BMI, HbA1c, and BUN. Results for the three age groups are plotted. There were 5776, 5317, and 5298 men (total 16,391) and 4890, 5730, and 6036 women (total 16,656) in the young (<45), middle-aged (45 - 59), and aged (59≤) groups, respectively. The subjects were further stratified into the five serum UA level groups defined in Figure 2. We have omitted the error bars for clarity but do comment here about the SD value of each plotted data point. For BMI, the SD values of all points/curves ranged from 2.6 - 3.4 for men and from 2.4 - 5.1 kg/m² for women, generally showing women > men differences. For HbA1c, the SD of all points/curves ranged from 0.6 - 1.4 for men and 0.4% - 0.9% for women, generally showing men > women differences. For BUN, the SD ranged from 3.1 - 4.0 for men, and 3.0 - 5.7 mg/dL for women.

HbA1c in women, the positive UA-HbA1c correlation was clearer in the aged group, suggesting more pronounced between-gender discordance in the UA-HbA1c relationship for the aged populations. For BUN in men, a strong association was found with age, but UA showed a negligibly weak association. For BUN in women, by contrast, both age and serum UA showed strong associations.

To assess the predictive ability of serum UA level and age for the presence of DM, dyslipidemia, and the MetS-like state, a logistic regression analysis was performed (**Table 3**). For all three conditions, the regression model using age as the sole explanatory variable led to an OR > 1 for both men and women, as predicted from previous reports. Intriguingly, the ORs for dyslipidemia and the MetS-like state in women were 1.04 (with 95% confidence interval (CI): 1.04 - 1.05) and 1.06 (1.05 - 1.06), respectively, which were both higher than the ORs for these conditions in men (**Table 3**), thereby implicating age as a more important risk factor in women than in men. For both men and women, the ORs for age remained largely unchanged after adjustment for serum UA. This suggested that the association between age and these conditions is strong and independent from predictions based on serum UA. In contrast, when the serum UA level was used as the sole explanatory variable, the model led to gender-divergent ORs, with the most remarkable difference being OR = 0.79 (95% CI: 0.75 - 0.83) in men and OR = 1.36 (1.25 - 1.47) in women in predicting DM (**Table 3**). The OR < 1 for DM in men was unsurprising given the negative correlation between serum UA and HbA1c (and FPG) shown in **Table 2** and **Figure 2**. Nonetheless, the OR was >1 for both dyslipidemia and the MetS-like state in men and women. Specifically, in women, serum UA showed strong associations with DM (OR = 1.36 (95% CI: 1.25 - 1.47)), dyslipidemia (OR = 1.86 (95% CI: 1.78 - 1.95)), and the MetS-like state (OR = 1.87 (1.79 - 1.96)). In men, after the adjustment for age, the OR for DM prediction increased slightly from 0.79 (0.75 - 0.83) to 0.81 (0.77 - 0.85), which suggested that age and serum UA did not substantially confound each other as risk factors for DM. For the MetS-like state in men, adjustment for age decreased the OR from 1.49 (1.38 - 1.46) to 1.34 (1.31 - 1.38); however, such a decrease was still greater in women, implying that age has a strong association with these conditions in women, and that the association between UA and glucose/lipids can be partly explained by the association between age and glucose. Nonetheless, after the adjustment for age, the ORs of serum UA increase in women were still significant for these conditions. For example, the age-adjusted model led to ORs of 1.34 (1.31 - 1.38) in men and 1.68 (1.60 - 1.76) in women for the MetS-like state, highlighting the higher predictive ability of serum UA in women relative to men.

We also performed an ROC analysis to further evaluate the ability of serum UA values to predict the presence of DM, dyslipidemia, and the MetS-like state. The AUC estimate for women was higher than that for men for all three conditions (**Figure 4**). In women, the suggested cut-off values were 5.1, 4.7 and 4.7 mg/dL for DM, dyslipidemia, and the MetS-like state, respectively; in men, these

Table 3. Odds ratios for a 1 mg/dL increase in serum UA and a 1 year increase in age (95% Confidence Interval) in logistic regression model-based association analysis for DM, dyslipidemia, and the MetS-like state.

		DM	Dyslipidemia	MetS-like state
Men	UA, unadjusted	0.79 (0.75 - 0.83)	1.41 (1.37 - 1.44)	1.49 (1.38 - 1.46)
	UA, age-adjusted	0.81 (0.77 - 0.85)	1.41 (1.37 - 1.44)	1.34 (1.31 - 1.38)
	age, unadjusted	1.05 (1.04 - 1.05)	1.00 (1.00 - 1.00)	1.01 (1.01 - 1.01)
	age, UA-adjusted	1.05 (1.04 - 1.05)	1.00 (1.00 - 1.00)	1.01 (1.01 - 1.01)
Women	UA, unadjusted	1.36 (1.25 - 1.47)	1.86 (1.78 - 1.95)	1.87 (1.79 - 1.96)
	UA, age-adjusted	1.13 (1.04 - 1.23)	1.71 (1.63 - 1.80)	1.68 (1.60 - 1.76)
	age, unadjusted	1.08 (1.07 - 1.09)	1.04 (1.04 - 1.05)	1.06 (1.05 - 1.06)
	age, UA-adjusted	1.08 (1.07 - 1.09)	1.03 (1.03 - 1.04)	1.05 (1.04 - 1.05)

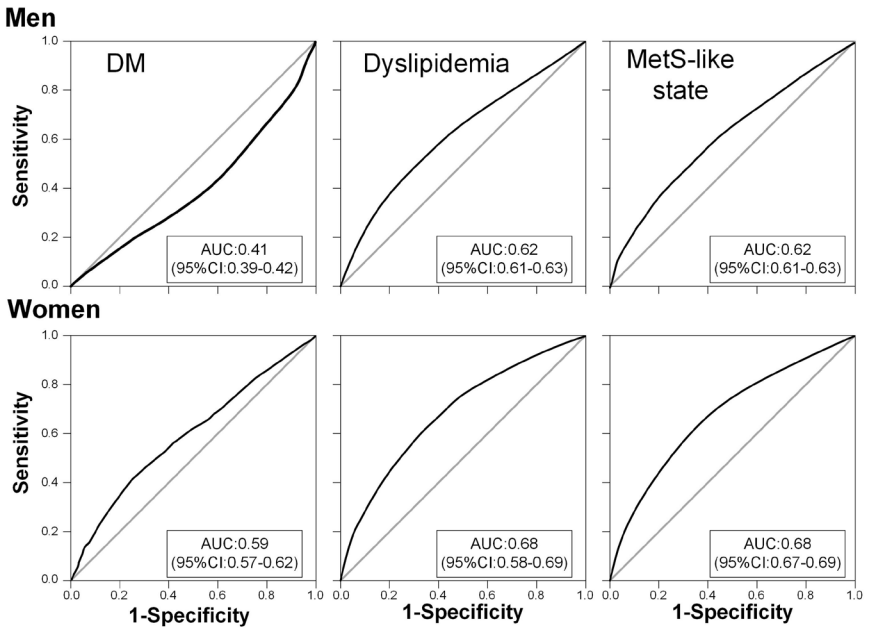

Figure 4. ROC analysis-based assessment of the ability of serum UA level to predict DM, dyslipidemia, and MetS-like state in women and men.

values were 6.6 mg/dL for dyslipidemia and 6.5 mg/dL for the MetS-like state. As we anticipated from the serum UA-HbA1c relationship seen in Figure 2, the use of serum UA as a predictor of DM in men was found to be inappropriate, suggesting that other biomarkers may be more suitable. Together, these results suggest that serum UA level is more useful as a marker for MetS and MetS-related conditions in women than in men. In men, the predictive ability of serum UA for DM appears to be severely limited.

To gain further insights into the effects of age on the associations between UA and the MetS-related conditions, the three age groups (<45, 45 - 59, 59≤) were compared in the ORs based on the logistic regression model analyses used in Table 3 (Table 4). As we expected from the results shown above, in women, the serum UA level showed good predictive ability for DM in the young group (OR = 1.75 (95% CI: 1.15 - 2.67)), but this ability was less clear for the middle-aged

Table 4. Comparison of the age-stratified groups in the odds ratios for a 1 mg/dL increase in serum UA and a 1 year increase in age (95% Confidence Interval) in logistic regression model-based association analysis for DM, dyslipidemia, and the MetS-like state.

		Odds ratio (95% CI)		
Age	**Sex**	**DM**	**Dyslipidemia**	**MetS-like state**
<45	**Men**	0.94 (0.82 - 1.08)	1.49 (1.42 - 1.56)	1.57 (1.50 - 1.65)
	Women	1.75 (1.15 - 2.67)	2.17 (1.91 - 2.47)	2.32 (2.01 - 2.68)
45 - 59	**Men**	0.78 (0.72 - 0.84)	1.38 (1.31 - 1.44)	1.40 (1.33 - 1.46)
	Women	1.13 (0.95 - 1.33)	1.85 (1.71 - 2.01)	1.85 (1.71 - 2.01)
59≤	**Men**	0.80 (0.75 - 0.85)	1.35 (1.29 - 1.42)	1.34 (1.28 - 1.40)
	Women	1.15 (1.05 - 1.27)	1.56 (1.47 - 1.67)	1.53 (1.44 - 1.63)

and aged groups. In men, the ORs for DM were lower than 1 reflecting the near-zero correlation coefficient between UA and FPG (Table 2), with the aged groups showing even smaller ORs. The predictive ability of serum UA for dyslipidemia (and the MetS-like state) was clearer in the young group for both men and women, and, in particular, the young women (OR = 2.17 (95% CI: 1.91 - 2.47) and 2.32 (2.01 - 2.68) for dyslipidemia and the MetS-like state, respectively). Overall, the results show that the effects of age on the association of serum UA with the MetS-related conditions were more pronounced for women than for men.

4. Discussion

In this cross-sectional study, we focused on the association between serum UA and various biomarkers in a Japanese population that had previously undergone a health check and observed the following findings. First, although serum UA levels were lower in women than in men, serum UA levels in women had a higher predictive ability for MetS-related conditions compared with men. This calls for consideration of the gender-specific clinical significance of serum UA as a risk factor for MetS. Second, a serum UA level around 5.0 mg/dL, which is lower than the conventional cut-off value, may serve as a useful cut-off for the risk assessment of MetS-related conditions in women in Japan. Third, correlations between serum UA level and fasting glucose, BUN, and BMI showed patterns that differed between men and women. Overall, our results support that menopause has profound effects on the association of UA with other clinical markers in women, calling for careful interpretation of the clinical significance of UA in postmenopausal women.

In our study, the mean serum UA value was higher in men than in women (6.1 versus 4.5 mg/dL, respectively) (Figure 1). These results are consistent with those of recent studies on Japanese adult populations, including one study by Kuwabara *et al.* [19], who reported a mean value of 6.2 mg/dL in men and 4.4 mg/dL in women [19] and another by Kawasoe *et al.* who reported values of 6.0 mg/dL and 4.5 mg/dL for men and women, respectively [20].

A number of studies have reported an association between hyperuricemia and diseases such as DM, dyslipidemia, hypertension, cardiovascular disease (CVD), and MetS [19] [21] [22]. Our findings corroborate with the previous findings that those with MetS have higher serum UA levels than those without the condition [3] [17] [23]. In one study by Hakoda *et al.*, the risk of death owing to CVD was more strongly associated with an increased UA level in women compared with men [24]. Our analysis using age-stratified subgroups (**Figure 3**) also corroborates the results presented by Li *et al.*, which found that the risk of MetS was higher in premenopausal women (OR = 3.42) than in postmenopausal women (OR = 1.87) in the highest quartile relative to the lowest quartile of serum UA [25].

At present, diagnosis of hyperuricemia in Japan is based on a serum UA level of 7.0 mg/dL or above, regardless of age and gender. Our study suggests that this cut-off level may predict MetS better if lowered for women. This idea has several precedents, including one study by Verdecchia *et al.*, which demonstrated that the operational serum UA cut-off value for cardiovascular event risk prediction in hypertensive patients was ≥4.6 mg/dL in women and ≥6.2 mg/dL in men [26]. In another cohort study, Alderman *et al.* suggested the values of ≥6.2 mg/dL in women and ≥7.5 mg/dL in men [27]. In our analysis, the suggested cut-off serum UA values in women were 5.1, 4.7, and 4.7 mg/dL for DM, dyslipidemia, and the MetS-like state, respectively, which are far smaller than the 7 mg/dL necessary for a hyperuricemia diagnosis in Japan. In contrast, our findings suggested limited usefulness of such cut-off values for men; while our analysis suggested 6.6 mg/dL for dyslipidemia and 6.5 mg/dL for the MetS-like state, seeking a cut-off value for DM in men was found to be inappropriate.

When age-dependent changes in serum UA levels (**Figure 1**) are considered, adjustments to these values, such as lowering the cut-off values for the elderly male population, may be necessary. However, in an analysis of a Korean population, AUC estimates were found to be more useful diagnostically for men in their 20s, 30s, and 40s than for those in their 70s, suggesting that use of UA levels to diagnose MetS may be more suitable for younger adult men [15]. Thus, in older men, risk factors other than UA may be more important as predictive factors for MetS [15].

Our results confirmed an earlier finding that serum UA levels are higher in men than age-matched women, supporting the view of a greater renal clearance of UA in women (**Figure 1**) [28] [29]. We also observed that serum UA largely decreased with age in men, but the opposite trend was seen in women (**Figure 1**). The molecular basis of such gender-specific changes of serum UA with age is not clear, but it may be at least in part explained by the hormonal regulation of gene expression. Estrogens have been shown to increase the fractional excretion of UA and reduce UA levels [28] [30]. In one mouse experiment, testosterone upregulated the expression of sodium-coupled monocarboxylate transporter 1 (Smct1), which functions to create a lactate gradient that drives serum UA reab-

sorption from glomerular filtrate through uric acid transporter 1 (URAT1, also referred to as SLA22A11), a UA-lactate exchanger [31]. Further, estrogen decreased the expression of SLC2A9 (also known as GLUT9, a mediator of serum UA flux across the anti-luminal side of the tubular epithelium), SLA22A11, and ABCG2 in the kidney [32], possibly reducing the renal reabsorption of UA.

Our analysis showed that high UA positively correlated with HbA1c and fasting glucose in women (**Figure 2**). The finding that men showed a weak correlation is counterintuitive, but this gender-divergence has similarities to previous reports; in both Chinese [33] and US [34] community-based studies, positive associations between HbA1c and serum UA levels were greater in women than in men. Choi and Ford showed that individuals, men in particular, with highly elevated HbA1c levels are at a *lower* risk of hyperuricemia. In contrast, women with moderately elevated HbA1c levels (*i.e.*, pre-diabetes) may be at a higher risk of hyperuricemia [34]. It has also been shown that high UA levels can impair insulin sensitivity [35]; however, it is largely unknown why such a gender difference occurs. In Choi and Ford, serum UA levels monotonically increased with insulin resistance, with a greater differential of insulin resistance corresponding to a 1 mg/dL difference of UA level in women relative to men. Insulin sensitivity has also been shown to be correlated with the renal clearance of UA [36] However, serum UA levels show a bell-curved relationship with fasting glucose (and HbA1c) level [34], likely because glycosuria acts to lower serum UA as DM progresses [34]. Similarly, Chino *et al.* showed that glucose stimulates serum UA transport by SLC2A9 (GLUT9) in the opposite direction [37], suggesting that SLC2A9 is involved in the glycosuria-induced reduction of serum UA, which has been observed in patients with type 2 DM. However, to what extent the SLC2A9-mediated transport of sugar and UA contribute to the gender-specific curves of serum UA and HbA1c is still unknown. As estrogen has genotype-specific effects on UA transport and estrogen improves insulin sensitivity [38] [39] [40], it is possible that the sex-dependent association between UA and glucose may be partly accounted for by the effect of estrogens on SLC2A9. It is plausible that this contributes to the positive association between HbA1c and UA in women in our study. However, the negative association observed in men cannot be explained well from such consideration. Nevertheless, it seems important to note that UA transport influences the transport of sugar and metabolic intermediates as well [41].

It is also plausible that there are other factors that serve to associate UA and glucose. Several studies employing the Mendelian randomization method have argued against the causative role of UA on incident DM [4] [42]. Moreover, in one study by Li *et al.*, their regression model indicated that although serum UA showed a correlation with DM incidence, UA was not significantly associated with DM incidence after adjustment of xanthine oxidase (XO) activity [41]. This evidence supports the view that UA is not causal for type 2 DM incidence. As XO is a major source of reactive oxygen species (ROS), the authors proposed

that oxidative stress resulting from elevated XO activity may cause DM [41] [43]. However, there appear to be several mechanisms that associate serum UA with oxidative stress, as discussed below.

In epidemiological studies, hyperuricemia has been shown to be associated with renal dysfunction [19] [44] [45]. In our analysis, subjects with higher levels of UA had a more severe decline in eGFR along with higher levels of creatinine (**Figure 2**). This was observed for both men and women, but was more pronounced in women, which remains consistent with several studies focused on gender differences in UA and kidney disease. For example, a cohort analysis of the general population in Okinawa by Iseki *et al.* showed that serum UA ≥ 6.0 mg/dL was an independent predictor of end-stage renal disease (ESRD) in women but was non-significant in men [46]. Combining two cohort studies (the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study), Weiner *et al.* showed that women, but not men, had higher incident kidney disease associated with higher UA levels [44]. In a study by Yang *et al.*, the multivariate-adjusted odds for CKD in the fourth UA level quartile were 6.05 in males and 8.21 in females, when compared with the first quartile [47]. Another interesting finding was that elevated serum UA was an independent risk factor for the progression of ESRD in female IgA nephritis patients but not in male patients, suggesting that women may be more vulnerable to UA-induced organ damage [48]. However, to our knowledge the molecular basis for such gender-differences is unknown. Estrogen promotes the excretion of UA, whereas androgens promote Smct1 expression [31]; therefore, menopause in women and physiological androgen level changes in men may have profound impacts on CKD. However, given the limited supporting evidence, further analysis addressing this between-gender difference is warranted.

Along with HbA1c (glucose), eGFR, and creatinine, UA levels in women showed pronounced correlations with BMI, blood pressure, and BUN. To our knowledge, the strong correlation between UA and BUN in women is a novel observation with an unclear molecular basis, warranting further investigation. The reason for such gender effects for BMI and blood pressure are also unclear. Nevertheless, it may be worthwhile to consider existing studies that utilize the genetic variant of SLC2A9 (GLUT9). SLC2A9 is a well-studied UA transporter that exhibits high gender-specific effects in its influence on serum UA levels [49]. Together with serum UA flux across the renal proximal tubule, SLC2A9 regulates UA level through its role in fructose homeostasis, thereby linking sugar to UA metabolism. An experiment by Witkowska *et al.* showed that the presence of extracellular hexose can increase the influx of UA through this transporter (SLC2A9a and SLC2A9b) [50]. Genetic variants of SLC2A9 have been extensively used in Mendelian randomization studies [4]. Notably, the association between SLC2A9 genotypes and UA levels was more pronounced in women than in men, and an increase in BMI amplified the effect of genetic variants on UA levels [51]. This may contribute to the more pronounced association of UA and BMI in women. Sex-dependent differences in the genotype-UA level association

have been shown for *SLC2A9* SNPs, with an association 2 - 3 times higher in women compared to men [52]. This study further showed that the effect on serum UA levels explained by *SLC2A9* genotypes increased linearly with age in women, whereas increasing age had a diminishing effect in men [52].

But why is the genetic effect of *SLC2A9* on UA level more pronounced in women? In Topless *et al.*, *SLC2A9* genotypes were not only associated with the average level of serum UA but also with the variance in UA levels in pre-menopausal women [53]. Such an association was not seen in post-menopausal women, suggesting that the effect of cyclical changes is a result of menstruation. Thus, female hormones and physiological factors affected by these hormones (such as iron levels and testosterone) may interact with SLC2A9 in a genotype-dependent manner. Mumford *et al.* showed that serum UA levels were highest during the follicular phase, were inversely associated with estradiol and progesterone, and were positively associated with FSH [54]. However, further analyses are necessary to assess the role of these transporters in sex-specific associations between UA and lipid/sugar biomarkers.

Another intriguing feature of the *SLC2A9* genotype is its drug sensitivity and interaction with salt transporters. Parsa *et al.* showed that the UA-increasing genotype of SLC2A9 was associated with higher blood pressure [55]. High UA levels may potentiate salt sensitivity, increasing blood pressure in individuals with a high-salt diet [55] [56]. However, further analyses are necessary to examine whether such properties contribute to gender differences in the UA-blood pressure relationship.

It has also been well established that UA is associated with obesity/adiposity. However, while obesity/adiposity has been increasingly implicated as a causal factor for hyperuricemia, the causality of the opposite association (*i.e.*, from UA to adiposity) has been poorly supported [4]. For instance, amelioration of insulin resistance through a low-energy diet or troglitazone led to a decrease in serum UA levels in overweight hypertensive patients [57]. Such a causal association between adiposity and increased UA was supported by bidirectional Mendelian randomization analysis conducted by Lyngdoh *et al.* [58]. However, the pathophysiological association between adiposity and UA increase has not been fully understood. Several studies have also focused on adipose tissue as a source of UA [59] [60]. One merit of this explanation is that it can explain a broad range of pathophysiological changes of MetS. Besides serum UA production in adipose tissue, it has been proposed that UA contributes to inflammation and oxidative stress in adipocytes, which in turn induces insulin resistance [61]. Of note, SLA22A11 (URAT1) is expressed in adipocytes, and UA absorbed by these adipocytes increases the level of ROS via the activation of NADPH oxidase, causing both inflammation and oxidative stress [62]. Additionally, Baldwin *et al.* showed that the administration of allopurinol to MetS model mice reduced adipocytokine secretion and insulin resistance [63]. Therefore, at least in some settings, both inflammation and oxidative stress may be induced by UA in adipocytes to cause abnormal adipocytokine secretion, leading to insulin resistance

and MetS development.

The present study has several limitations. First, the cross-sectional approach does not allow for inference of the causal effects of UA. As we mentioned above, genetic approaches suggest that UA is a biomarker rather than a causal element, but the possibility that it has causal effects in some settings cannot be ruled out. Second, the dataset used did not contain information concerning UA-lowering drugs or diet, hampering analyses of such effects on MetS.

5. Conclusion

In conclusion, this study suggested that serum UA level is a more useful marker for MetS and MetS-related conditions in women compared with men in a population of individuals involved in a health screening in Japan. A serum UA level around 5.0 mg/dL appears to serve as a useful cut-off value for the risk assessment of MetS-related conditions in women in Japan. In men, serum UA was not found to be useful as a predictive parameter for DM.

Author Contributions

Conceptualization: Inoue K., Seki R. Statistical analysis: Seki R., Kimura T. Writing original draft preparation: Seki R. Writing review and editing: Inoue K. Approval of final manuscript: all authors.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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