原著 2

Determinants of serum uric acid in community-dwelling elderly Japanese women

Ayaka Tsuboi¹⁾ Mayu Terazawa-Watanabe²⁾
Tsutomu Kazumi^{1,4)} Keisuke Fukuo^{1,3)}

Aim

Determinants of serum uric acid (SUA) levels in relation to kidney function have not been extensively studied in elderly Japanese people.

Design

In this cross-sectional study, relationships of SUA with anthropometric indices, serum adipokines and liver enzymes, insulin-resistance related variables and inflammatory markers in relation to kidney function were examined in 159 community-dwelling elderly Japanese women.

Results

By simple linear regression analysis, serum creatinine and cystatin C were positively and eGFR was inversely associated with SUA. It was also positively associated with BMI, percentage body fat, serum leptin and transthyretin. In addition, SUA showed positive associations with fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR) and serum gamma-glutamyltransferase (GGT). Further, log high-sensitivity C-reactive protein (hsCRP) and tumor necrosis factor-alpha (TNF- α) were

associated with SUA. Multiple regression analysis with SUA as a dependent variable showed that 27% of the variability of SUA can be accounted for by serum creatinine, GGT, leptin and transthyretin in order of increasing R².

Conclusions

In elderly Japanese non-obese women, high serum uric acid levels may represent a more favorable nutritional status and increased body fat in addition to poorer renal function. Associations with serum creatinine and GGT warrant further study.

High serum uric acid (SUA) is one of the best independent predictors of type 2 diabetes and commonly precedes the development of both insulin resistance and diabetes.¹⁾ An elevated SUA also independently predicts the development of fatty liver,²⁾ obesity,³⁾ hypertension⁴⁾ and elevations in C-reactive protein (CRP).⁵⁾ Furthermore, metabolic syndrome is associated with a high frequency of hyperuricemia, and similarly, hyperuricemia is associated with metabolic syndrome.^{6, 7)} Many of

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1) Postgraduate School of Food Sciences and Nutrition

2) Department of Food Sciences and Nutrition, School of Human Environmental Sciences

3) Research Institute for Nutrition Sciences, Mukogawa Women's University, 6-46, Ikebiraki-cho, Nishinomiya, Hyogo 663-8558, Japan,

4) Diabetes Center, Myodani Hospital, 2350-2, Aza Nashihara, Myodani-cho, Tarumi-ku, Kobe, Hyogo 655-0852, Japan

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these studies were conducted mainly in middle-aged and male populations, and correlates of SUA levels have not been extensively studied in elderly Japanese people.

Reduced renal function and high SUA are associated with each other and are common in the elderly.^{8, 9)} As SUA levels are higher in postmenopausal as compared to premenopausal women,^{10, 11)} we investigated associations of SUA with serum levels of hepatic enzyme and adipokines, markers of adiposity, insulin resistance, and inflammation, and components of metabolic syndrome in community-dwelling postmenopausal elderly women.

Subjects and Methods

We examined 159 free-living elderly women who have been reported elsewhere.¹²⁾ They were residents in Nishinomiya City and were recruited as volunteers by local welfare commissioners from the city of Nishinomiya, Hyogo, Japan. Although 43, 9 and 58 women (27.0, 5.7, and 36.5%, respectively) reported to be receiving statins, anti-diabetic and anti-hypertensive drugs, respectively, detailed drug information was not available. Subjects with clinically diagnosed acute or chronic inflammatory diseases, endocrine, cardiovascular, hepatic, or renal diseases, taking hormonal contraception, or showing unusual dietary habits were excluded from the study. This research followed the tenets of the Declaration of Helsinki. The design of this study was approved by the Ethical Committees of Mukogawa Women's University and written informed consent was obtained from all participants.

Anthropometric indices and blood pressure were measured after an overnight fasting as previously reported.¹²⁾ Thereafter, blood samples

were obtained from the cubital vein. Fat mass was measured using an impedance method (InBody 430, Biospace, Tokyo, Japan).

We evaluated routine chemical parameters, including liver enzymes and albumin. Plasma glucose, serum insulin, lipids and lipoproteins were assayed as previously reported^{13, 14)} and insulin resistance was evaluated using homeostasis model assessment (HOMA-IR).¹⁵⁾ Low-density lipoprotein (LDL) cholesterol was determined using Friedewald's formula.¹⁶⁾ Serum transthyretin (TTR), also called prealbumin, was measured as previously reported.¹⁷⁾

Adiponectin was assayed with a sandwich enzyme-linked immunosorbent assay (Otsuka Pharmaceutical Co., Ltd., Tokushima City, Japan). Intra- and inter- assay CV were 3.3% and 7.5%, respectively. Leptin was assessed using a RIA kit from LINCO Research (St. Charles, MO, USA, inter-assay CV=4.9%). High-sensitivity CRP (hs-CRP) was measured by an immunoturbidometric assay with the use of reagents and calibrators from Dade Behring Marburg GmbH (Marburg, Germany; interassay CV<5%). Tumor necrosis factor- α (TNF- α) was measured by immunoassays (R&D Systems, Inc., Minneapolis, MN, USA, interassay CV<6%). Plasminogen activator inhibitor-1 (PAI-1) was measured by an ELISA method. (Mitsubishi Chemicals, interassay CV<8%). The complete blood cell count was analyzed using an automated blood cell counter (Sysmex XE-2100, Sysmex, Kobe, Japan).

Serum creatinine and uric acid were measured enzymatically using an Autoanalyzer (AU 5200, Olympus, Tokyo, Japan) and cystatin C was measured by latex immunoassay using a commercially available kit (IatroCys-C, Mitsubishi Chemical Medience, Tokyo, Japan). The estimated glomerular filtration rate (eGFR)

Table 1. Anthropometric and biochemical characteristics of 159 free-dwelling women studied and correlation coefficients of serum uric acid.

	Mean $\pm$ SD	serum uric acid	
		simple	partial
Age (years)	75.6 $\pm$ 8.0	-.063	-.376 ***
BMI (kg/m ²)	22.6 $\pm$ 2.9	.235 **	.234 **
Body fat percentage (%)	33.0 $\pm$ 6.9	.171 *	.128
SBP (mmHg)	143.4 $\pm$ 19.0	.089	-.018
DBP (mmHg)	84.4 $\pm$ 10.4	.070	.038
Albumin (g/dl)	4.4 $\pm$ 0.3	-.044	.073
Transthyretin (mg/dl)	28.2 $\pm$ 4.8	.185 *	.242 **
ALT (U/l)	19.3 $\pm$ 16.6	.111	.200 *
GGT (U/l)	25.0 $\pm$ 15.9	.252 **	.299 ***
Plasma glucose (mg/dl)	100 $\pm$ 29	.134	.105
Insulin (μ U/ml)	8.3 $\pm$ 7.5	.160 *	.089
log insulin	0.7 $\pm$ 0.2	.213 **	.149
HOMA-IR	1.23 $\pm$ 1.08	.163 *	.083
log HOMA-IR	0.002 $\pm$ 0.256	.221 **	.158
Total cholesterol (mg/dl)	219 $\pm$ 31	-.096	-.023
HDL-cholesterol (mg/dl)	64 $\pm$ 14	-.116	-.056
nonHDL-cholesterol (mg/dl)	155 $\pm$ 33	-.042	.004
Triglyceride (mg/dl)	119.2 $\pm$ 64.9	.003	-.015
Serum uric acid (mg/dl)	4.8 $\pm$ 1.0	1.000 ***	1.000 ***
Serum creatinine (mg/dl)	0.69 $\pm$ 0.15	.412 ***	.235 **
Cystatin C (mg/l)	0.85 $\pm$ 0.20	.343 ***	.043
eGFRaver (ml/min/1.73 m ²)	71.1 $\pm$ 15.9	-.348 ***	adjusted
Leptin (ng/ml)	7.7 $\pm$ 4.7	.296 ***	.245 **
Adiponectin (μ g/ml)	14.1 $\pm$ 7.8	-.088	-.154
hsCRP (μ g/dl)	85 $\pm$ 109	.071	.031
log hsCRP	1.71 $\pm$ 0.42	.165 *	.110
TNF- α (pg/ml)	1.6 $\pm$ 1.0	.218 **	.066
PAI-1 (ng/ml)	26.5 $\pm$ 16.5	.132	.173 *
IL-6 (pg/ml)	5.5 $\pm$ 12.0	.133	.077
White blood cells ($\times 10^3/\mu$ l)	6.1 $\pm$ 1.6	.033	-.043

BMI : body mass index, FMI: fat mass index, GGT : γ -glutamyltransferase, eGFR : estimated glomerular filtration rate, hsCRP : high- sensitivity CRP, TNF- α : tumor necrosis factor- α , PAI-1 : plasminogen activator inhibitor-1, IL-6 : interleukin-6. *, p<0.05, **, p<0.01, ***, p<0.001.

was calculated using the equation recommended by the Japanese Society of Nephrology.^{18, 19)} The average of creatinine-based and cystatin-C based eGFR was calculated in each participant. Average eGFR has been recommended for estimation of renal function in elderly populations²⁰⁾ and therefore, was used in statistical analysis in the present study. Reduced kidney function^{18, 19)} was defined as eGFR < 60 ml/min/1.73m².

Data are presented as the mean $\pm$ SD unless otherwise stated. Due to deviation from a normal distribution, insulin, HOMA-IR and hsCRP were logarithmically transformed for analysis. Differences between 2 groups were analyzed by t test and frequencies of conditions by the Chi-square test. Differences among 3 groups were analyzed using analysis of variance. When p values in analysis of variance were $p < 0.05$, Bonferroni's multiple comparison procedure was performed. Correlations of SUA were evaluated by Pearson correlation analysis. Stepwise multiple regression analyses were performed to further identify the most significant variables contributing to the variation of SUA. Potential confounders or variables of interest were forced into the model and standardized β coefficients were calculated. The explanatory power of the model was expressed as adjusted R² values. A two-tailed $p < 0.05$ was considered significant. All calculations were performed with SPSS system 15.0 (SPSS Inc, Chicago, IL, USA).

Results

As previously reported,¹²⁾ participants were apparently healthy, community-dwelling elderly women (Table 1). SUA averaged 4.8 ± 1.0 mg/dl and $\text{SUA} \geq 6.0 \text{ mg/dl}$ ¹⁰ was found in 22 women (13.8%) whereas there were only 3

women (1.9%) with $\text{SUA} \geq 7.0$ mg/dl. Of 159 women, 104 (65.4%) had hypertension (on anti-hypertensive medication or systolic blood pressure (SBP)/diastolic blood pressure (DBP) $\geq 140/90$ mmHg without medication) and SBP/DBP averaged 143/84 mmHg. In contrast, obesity ($\text{BMI} \geq 25.0$ kg/m²) was found in only 16.4% (26 women) and the average BMI was 22.6 kg/m². Reduced kidney function was noted in 32 women (20.1%).

In simple linear regression analysis (Table 1), SUA was associated positively with serum creatinine and cystatin C, and inversely with average eGFR. It was positively associated with body fat percentage, serum leptin, HbA1c, log insulin and log HOMA-IR. In addition, SUA was associated with log hsCRP and TNF- α . Furthermore, it was associated with TTR and GGT. However, SUA was not associated with serum triglycerides, HDL cholesterol or blood pressure. After adjustment for average eGFR (Table 1), the association with creatinine remained significant although that with cystatin C turned to be non-significant. Associations with age, alanine aminotransferase (ALT) and PAI-1 turned to be significant. However, association with age was not positive but inverse. Although associations with log insulin, log HOMA-IR, log hsCRP and TNF- α became insignificant, associations remained significant with BMI, percentage body fat, leptin, HbA1c, GGT and TTR after adjustment for average eGFR.

We have done multiple regression analysis with SUA as a dependent variable, which included average eGFR and all variables that showed significant associations with SUA after adjustment for average eGFR as independent variables (Table 2, model A). Serum creatinine and leptin as well as GGT and TTR were determinants of SUA independently of renal

Table2 Stepwise multiple regression analysis with serum uric acid as dependent variable in community-dwelling elderly women

model A	Standardized β	p value	cumulativeR ²
serum creatinine	0.359	<0.001	0.182
GGT	0.193	0.007	0.223
leptin	0.189	0.011	0.255
transthyretin	0.148	0.038	0.272
model B			
serum creatinine	0.361	<0.001	0.182
GGT	0.199	0.006	0.223
leptin	0.198	0.008	0.255

Data are standardized β . Model A included all variables which showed significant associations with uric acid after controlling for average estimated glomerular filtration rate (eGFR) in Table 1; age, BMI, percentage body fat, ALT, GGT, leptin, PAI-1, transthyretin, HbA1c, creatinine and an average of creatinine-based and cystatin-based eGFR in Table 1. In Model B, all parameters which showed significant differences between women with and without hyperuricemia after controlling for average eGFR were included; age, BMI, percentage body fat, pre-heparin lipoprotein lipase, log hsCRP, GGT, leptin, creatinine and an average of creatinine-based and cystatin-based eGFR.

function and inflammatory markers in community-living elderly women. These 4 variables explained 27.2% of SUA variability.

Because it has been reported that women with $\text{SUA} \geq 6.0\text{mg/dl}$ have an increased risk of end-stage kidney disease,⁸⁾ elderly women were divided into 2 groups (Table 3). Elderly women with $\text{SUA} \geq 6.0\text{mg/dl}$ as compared to women with $\text{SUA} < 6.0\text{mg/dl}$ had higher BMI, body fat percentage and serum leptin. Serum creatinine and cystatin C were also higher and eGFR was lower in women with elevated SUA. Log insulin and log HOMA-IR were marginally higher in women with elevated SUA although there was no difference in blood pressure or the proportion of women on antihypertensive drugs (72.7 and 64.2% of women with and without elevated SUA, respectively, $p=0.43$). Furthermore, women with elevated SUA had higher GGT, log hsCRP and

TNF- α . After controlling for average eGFR, the difference in age turned to be significant: women with $\text{SUA} \geq 6.0\text{mg/dl}$ were younger, not older than those with $\text{SUA} < 6.0\text{mg/dl}$ (70.3 ± 1.4 vs. 76.5 ± 0.5 (standard errors) years old, $p < 0.001$). Differences remained significant for BMI, percentage body fat, leptin, creatinine, eGFR, log hsCRP and GGT although significant differences in log insulin, log HOMA-IR and log TNF- α were abolished (data not shown).

Multiple regression analysis with SUA as a dependent variable and average eGFR and all parameters which showed significant differences between women with and without hyperuricemia after controlling for average eGFR as independent variables (Table 2, model B), showed that 25.5% of the SUA variability can be accounted for by serum creatinine, GGT and leptin in order of increasing R².

Table 3. Anthropometric and biochemical characteristics of women with elevated uric acid (≥ 6.0 mg/dl)

	Not elevated			elevated			P-value
	n=137			n=22			
Age (years)	75.8	±	8.0	74.5	±	8.6	0.484
BMI (kg/m²)	22.2	±	2.8	24.4	±	3.1	0.001
Body fat percentage (%)	32.4	±	6.9	36.4	±	6.0	0.013
SBP (mmHg)	142.9	±	19.2	146.3	±	18.5	0.450
DBP (mmHg)	84.4	±	10.7	84.7	±	8.4	0.899
Albumin (g/dl)	4.4	±	0.3	4.4	±	0.3	0.546
Transthyretin (mg/dl)	28.1	±	4.8	28.7	±	5.1	0.543
ALT (U/l)	18.5	±	9.8	19.6	±	10.7	0.623
GGT (U/l)	23.4	±	14.6	34.5	±	19.9	0.019
Plasma glucose (mg/dl)	87	±	13	89	±	14	0.488
Insulin (μ U/ml)	5.3	±	3.6	6.9	±	6.1	0.085
log insulin	0.66	±	0.23	0.76	±	0.23	0.050
HOMA-IR	1.18	±	0.98	1.56	±	1.56	0.135
log HOMA-IR	-0.013	±	0.256	0.100	±	0.244	0.054
Total cholesterol (mg/dl)	223	±	32	208	±	34	0.049
HDL-cholesterol (mg/dl)	67	±	16	62	±	15	0.196
nonHDL-cholesterol (mg/dl)	156	±	32	146	±	30	0.164
Triglyceride (mg/dl)	120.3	±	67.0	112.0	±	50.9	0.582
Serum uric acid (mg/dl)	4.5	±	0.8	6.6	±	0.4	0.000
Serum creatinine (mg/dl)	0.70	±	0.15	0.87	±	0.17	0.000
Cystatin C (mg/l)	0.83	±	0.19	0.99	±	0.23	0.001
eGFRmean (ml/min/1.73m²)	73.0	±	15.5	59.1	±	12.5	0.000
Leptin (ng/ml)	8.6	±	5.8	12.7	±	7.5	0.003
Adiponectin (μ g/ml)	16.0	±	7.5	14.9	±	7.0	0.548
hsCRP (μg/dl)	193	±	335	339	±	529	0.222
log hsCRP	1.84	±	0.59	2.18	±	0.53	0.013
TNF- α (pg/ml)	0.3	±	0.2	0.4	±	0.2	0.007
PAI-1 (ng/ml)	28.8	±	11.3	30.2	±	8.5	0.570
IL-6 (pg/ml)	4.7	±	6.0	10.5	±	28.7	0.360
White blood cells (× 10³/μ l)	5.8	±	1.3	6.0	±	2.0	0.633

Data are mean $\pm$ SD. Abbreviations are the same as in Table 1.

Table 4. Anthropometric and biochemical characteristics of women according to tertiles of serum uric acid.

	Low	Medium	High
	2.5-4.2	4.3-5.0	5.1-7.6
	n=50	n=52	n=57
Age (years)	76.6 ± 7.1	74.3 ± 8.7	76.0 ± 8.2
BMI (kg/m ²)	22.2 ± 2.5 ^a	21.8 ± 2.9 ^a	23.5 ± 3.1 ^b
Body fat percentage (%)	32.2 ± 6.6 ^a	31.5 ± 6.7 ^a	35.0 ± 6.9 ^b
SBP (mmHg)	141.1 ± 18.1	143.9 ± 18.7	144.9 ± 20.4
DBP (mmHg)	83.3 ± 9.8	85.3 ± 11.3	84.6 ± 10.1
Albumin (g/dl)	4.4 ± 0.3	4.5 ± 0.2	4.4 ± 0.3
Transthyretin (mg/dl)	26.7 ± 4.3 ^a	28.8 ± 5.1 ^b	28.9 ± 4.8 ^b
ALT (U/l)	16.6 ± 7.0	19.0 ± 9.2	20.1 ± 12.3
GGT (U/l)	20.9 ± 9.6 ^a	22.6 ± 9.6 ^a	30.7 ± 22.2 ^b
Plasma glucose (mg/dl)	84.9 ± 7.7	89.7 ± 10.8	88.3 ± 17.0
Insulin (μU/ml)	5.2 ± 4.5	5.0 ± 2.4	6.2 ± 4.7
log insulin	0.63 ± 0.25 ^a	0.65 ± 0.20 ^{ab}	0.72 ± 0.23 ^b
HOMA-IR	1.12 ± 1.06	1.12 ± 0.59	1.43 ± 1.40
log HOMA-IR	-0.052 ± 0.272 ^a	-0.003 ± 0.217 ^{ab}	0.055 ± 0.268 ^b
Total cholesterol (mg/dl)	222.5 ± 29.6 ^{ab}	227.5 ± 29.7 ^a	212.6 ± 26.8 ^b
HDL-cholesterol (mg/dl)	68.5 ± 16.2	65.8 ± 13.3	65.0 ± 17.1
nonHDL-cholesterol (mg/dl)	153.9 ± 24.5 ^{ab}	161.8 ± 30.4 ^a	147.6 ± 36.9 ^b
Triglyceride (mg/dl)	121.5 ± 73.1	120.9 ± 63.1	115.5 ± 59.7
Serum Uric acid (mg/dl)	3.6 ± 0.5 ^a	4.7 ± 0.2 ^b	5.9 ± 0.6 ^c
Serum creatinine (mg/dl)	0.66 ± 0.10 ^a	0.70 ± 0.15 ^a	0.81 ± 0.18 ^b
Cystatin C (mg/l)	0.77 ± 0.11 ^a	0.85 ± 0.22 ^a	0.93 ± 0.22 ^b
eGFR _{mean} (ml/min/1.73m ²)	76.8 ± 15.4 ^a	73.6 ± 17.0 ^a	63.9 ± 14.9 ^b
Leptin (ng/ml)	7.4 ± 4.3	9.0 ± 5.7	10.9 ± 7.5
Adiponectin (μg/ml)	16.3 ± 6.4	16.6 ± 9.2	14.7 ± 6.2
hsCRP (μg/dl)	230.9 ± 338.6	163.8 ± 377.5	243.6 ± 388.0
log hsCRP	1.821 ± 0.698	1.804 ± 0.509	2.010 ± 0.556
TNF-α (pg/ml)	1.98 ± 0.91 ^a	2.41 ± 1.08 ^{ab}	2.52 ± 1.57 ^b
PAI-1 (ng/ml)	27.4 ± 9.7	28.7 ± 11.4	30.7 ± 11.4
IL-6 (pg/ml)	3.89 ± 4.25	5.83 ± 8.03	6.66 ± 18.12
White blood cells (×10 ³ /μl)	5.7 ± 1.3	5.7 ± 1.4	6.0 ± 1.6

Data are mean ± SD. Abbreviations are the same as in Table 1. Means not sharing common letters are significantly different each other at p<0.05 or less

In order to further confirm the correlations of SUA, elderly women were divided into 3 groups according to the tertiles of SUA (Table 4). Women in the top tertile had higher BMI, percentage body fat and log GGT than those in the other 2 groups. The prevalence of women on anti-diabetic medication was higher in the top ($n=8$, 14.0%) compared to the median and bottom SUA tertiles ($n=1$, 1.9 and 0%, respectively, $p=0.003$). In addition, HbA1c, log insulin, log HOMA-IR and log ALT were higher in women in the top as compared to the lowest SUA tertile. Furthermore, women in the median and top as compared to the lowest SUA tertile had higher TTR and log TNF- α . Associations with BMI, TTR, HbA1c, GGT and ALT remained significant after controlling for average eGFR (data not shown). There was no difference in SBP, DBP and lipid and lipoprotein levels or the prevalence of women receiving statin and anti-hypertensive drugs.

Discussion

To the best of our knowledge, this is the first report assessing the relationship of SUA with anthropometric indices, serum adipokines, insulin-resistance related, inflammatory and hematological variables in elderly Japanese women. The present study demonstrated that higher SUA was associated with higher serum levels of creatinine, GGT, leptin and TTR in elderly Japanese women. These associations were independent of renal function, insulin resistance and inflammation. We confirmed the previous findings that high SUA is associated with reduced renal function^{8, 9)} and high serum leptin levels.^{21, 22)} It is noteworthy that these findings were observed in community-dwelling elderly women who had fewer indicators of disease, such as a low BMI, hypoalbuminemia

and hypocholesterolemia.

Serum creatinine was the strongest correlate of SUA independent of kidney function in elderly Japanese women as previously reported in middle-aged Japanese males.²³⁾ Baseline concentrations of, and 10 year changes in SUA were associated with baseline concentrations of, and changes in serum creatinine in young women.²⁴⁾ Although underlying mechanisms of these associations remain unclear, it has been suggested that the skeletal muscles, a source of serum creatinine, may be an important source of uric acid in the circulation in hypertensive patients.²⁵⁾ Hypertension was observed in 104 (65.4%) of the 159 women studied in the present study.

While uric acid has pro-oxidative effects inside the cell, it is an antioxidant in the extracellular environment.¹⁾ Recently, serum GGT concentrations have become regarded as a marker of oxidative stress.²⁶⁾ A recent epidemiological study in Japanese men showed that increased serum GGT is an independent predictor of the subsequent development of hyperuricemia.²⁷⁾ Taken together, these findings may provide a rationale for the positive association between GGT and SUA and suggest that oxidative stress may play a key role in this relationship.²⁷⁾

An elevated uric acid cross-sectionally is associated with BMI²⁸⁾ and independently predicts future weight gain or obesity.³⁾ As previously reported in obese or diabetic people^{29, 30)} and non-obese Japanese middle-aged women,³¹⁾ and confirmed in the present study of elderly non-obese women, serum leptin, a marker of the amount of adipose tissue in the body,³²⁾ was a determinant of SUA independent of BMI, percentage body fat, kidney function and insulin resistance (HOMA-IR). Although

the underlying mechanisms of the association between SUA and leptin remained unclear. Bedir A et al.²⁹⁾ recently discussed the role of leptin as possibly being a regulator of SUA concentrations in humans and suggested that leptin might be one of the possible candidates for the missing link between obesity and hyperuricemia.

Because TTR is a useful marker of malnutrition in the elderly,³³⁾ a significant and independent association between TTR and SUA in the present study may represent more favorable nutrition in elderly women with higher SUA. However, it is interesting that 5-hydroxyisourate hydrolase, another enzyme participating urate degradation to allantoin,³⁴⁾ and TTR, a carrier protein involved in the extracellular transport of thyroid hormones and in the co-transport of retinol, are closely related phylogenetically and structurally.³⁵⁾ It has been shown that a small number of critical mutations affecting the active site of the enzyme may be sufficient to generate the markedly different function.³⁵⁾

Adjustment for kidney function abolished the association of SUA with fasting insulin and HOMA-IR, and with inflammatory markers in the current study. The former may be in accordance with data suggesting that renal insufficiency suppresses renal clearance of insulin, leading to its higher circulating levels.³⁶⁾ The latter finding may be in line with the observation that inflammatory biomarkers are elevated in elderly persons with renal insufficiency.³⁷⁾

Elevated SUA has been shown to be associated with low-grade inflammation in Caucasian population-based study³⁸⁾ and Italian elderly cohort.³⁹⁾ However, decreases in SUA with accompanying increased urinary excretion

of uric acid were associated with 2 conditions of clinically overt inflammation: during gouty attack⁴⁰⁾ and after the exogenous administration of human recombinant IL-6 in cancer patients⁴¹⁾ A modest elevation of IL-6 may be a consequence of modest increases in SUA in the former^{5, 38, 39)} whereas markedly elevated IL-6 may be a cause of a decrease in SUA in the latter.^{40, 41)}

In 2487 middle-aged Japanese men,²³⁾ serum creatinine was the strongest correlate of SUA, followed by serum TG, BMI and diastolic blood pressure. In 916 Japanese elderly women,⁴²⁾ with increasing SUA, TG levels and diastolic blood pressure increased and HDL cholesterol decreased even in the absence of metabolic syndrome. In the present study, however, we did not find associations with serum lipids and blood pressure. This may be in part due to small sample size in our study.

Several limitations must be acknowledged. The cross-sectional design of this study does not allow for the identification of causal relationships. The recruitment procedure may also have had an impact on the results. As participation was voluntary, women who pay more attention to their health may have been more likely to participate. Biochemical parameters, including SUA levels, were measured only once. Although 58 women (36.5%) reported to be receiving anti-hypertensive drugs information regarding diuretics was not available; therefore, the possible contribution of diuretics or other drugs to SUA levels⁴³⁾ or other parameters cannot be completely excluded. Sakaki and Tsuchihashi⁴⁴⁾ reported that diuretics were administered in 22% of patients on anti-hypertensive drugs.

In spite of these limitations, the present study is the first to examine determinants of uric acid

in elderly Japanese women. High serum uric acid levels may represent a more favorable nutritional status and increased body fat in addition to poorer renal function in Japanese postmenopausal women. Associations with serum creatinine and GGT warrant further study.

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