Serum Uric Acid Is Associated With the Left Ventricular Mass Index in Males of a General Population

Ayako YOSHIMURA,¹ MD, Hisashi ADACHI,² MD, Yuji HIRAI,¹ MD, Mika ENOMOTO,¹ MD, Ako FUKAMI,¹ MD, Eita KUMAGAI,¹ MD, Kyoko OHBU,¹ MD, Sachiko NAKAMURA,¹ MD, Aya OBUCHI,¹ MD, Yume NOHARA,¹ MD, and Tsutomu IMAIZUMI,¹ MD

SUMMARY

The association of serum uric acid (UA) with left ventricular hypertrophy (LVH) remains controversial. We investigated this issue in a general population. Participants consisted of 1,943 subjects (774 males and 1,169 females) aged over 40 years, living in Tanushimaru (a Japanese cohort of the Seven Countries Study). Serum UA and other biochemistry parameters were determined by a standard analytical technique. All individuals underwent anthropometric measurements and 2-dimensional echocardiography. Because serum UA levels are much higher in males than in females, they were analyzed separately. When LV mass index (LVMI) levels were stratified according to tertile as low ($\leq 80 \text{ cm}^2$; $n = 261$), middle ($81\text{--}103 \text{ cm}^2$; $n = 261$), and high ($\geq 104 \text{ cm}^2$; $n = 252$) in males, there were significant relationships between LVMI and UA, in addition to age, body mass index, systolic blood pressure, medication for hypertension, triglycerides, and alcohol intake. Multiple stepwise regression analysis revealed LVMI was significantly associated with systolic BP ($P < 0.0001$), medication for hypertension ($P < 0.0001$), UA ($P = 0.003$), BMI ($P = 0.019$), and alcohol intake ($P = 0.038$) in males. In females, LVMI was not associated with UA. In a multiple logistic regression analysis, a significantly higher odds ratio of LVH (odds ratio: 1.77, 95%CI: 1.01–3.09, $P < 0.05$) was observed for males in the highest UA tertile versus the lowest UA tertile after adjustments for confounding factors, but not for females. In this cross-sectional study, there was a clear difference in the relation of UA and LVH between males and females. High serum UA was significantly and independently associated with LVH evaluated by echocardiography in only males of a general population. (Int Heart J 2014; 55: 65–70)

Key words: Epidemiology, Echocardiography

Left ventricular hypertrophy (LVH) is an independent and powerful risk factor for cardiovascular events and death.^{1,2} Uric acid (UA) may induce LVH and the following mechanisms have been proposed.³ UA induces inflammatory and proliferative cytokines like tumor necrosis factor- α and mitogen-activated protein kinases,^{4–6} which promote cardiac hypertrophy. UA also activates the renin-angiotensin-aldosterone system,^{7–10} which is a well-known system for hypertrophy and hyperplasia of myocytes and fibrosis of the heart. Thus, it may be interesting to study in humans whether UA is associated with LVH. Several such studies have been performed.^{11–15} However, the results have not been consistent. Some studies reported a positive association only in males^{14,15} and others reported such an association only in females.¹³ In some studies,^{11,13,15} the enrolled subjects were only hypertensive while in others,^{12,14} they were apparently healthy subjects. Nowadays, many subjects are taking antihypertensive medications. Thus, data must be analyzed after adjustment for confounders like gender, hypertension, and others. Furthermore, in many studies,^{14,16} LVH was measured by electrocardiography

(ECG), and in a few studies,^{12,13} it was measured by echocardiography; it is well known that ECG is less sensitive than echocardiography for detection of LVH.¹⁷ Therefore, in this study, we investigated the association between serum UA and LVH evaluated by echocardiography in a general population.

METHODS

Study population: In 2009, we carried out physical examinations on the inhabitants of Tanushimaru in Fukuoka (a cohort of the Seven Countries Study).^{18,19} The Seven Countries Study is an epidemiologic population-based study that started in the late 1950s. Originally, the study aimed to examine the relationship between cholesterol and incident coronary artery disease. In 16 international cohorts, males aged 40–59 years were enrolled between 1958 and 1964. In Japan, two cohorts, Tanushimaru and Ushibuka, were selected. The Tanushimaru cohort consisted predominantly of farmers, whereas the Ushibuka cohort consisted mainly of fishermen. Although The Seven

From the Departments of ¹ Internal Medicine, Division of Cardio-Vascular Medicine and ² Community Medicine, Kurume University School of Medicine, Fukuoka, Japan.

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Address for correspondence: Hisashi Adachi, MD, Department of Community Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan. E-mail: hadac@med.kurume-u.ac.jp

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Countries Study ended in 1989, we continued the epidemiologic study in Tanushimaru. Informed consent was obtained from all subjects in accordance with the ethics committee guidelines of our university. As reported previously, the demographic backgrounds of the subjects in this area are similar to those of the Japanese general population.^{18,19} We examined 1,943 persons over the age of 40 years (774 males and 1,169 females).

Data collection: The medical history, use of alcohol, and smoking were ascertained by a questionnaire. Alcohol intake and smoking were classified as current habitual use or not. Height and weight were measured, and body mass index (BMI) was calculated as weight (kilograms) divided by the square of height (square meters) as an index of obesity. Waist circumference was measured at the level of the umbilicus in the standing position. Blood pressure (BP) was measured in the supine position twice at 3-minute intervals using an upright standard sphygmomanometer. Vigorous physical activity and smoking were avoided for at least 30 minutes before BP measurement. The second BP with the fifth-phase diastolic pressure was used for analysis. Hypertensive subjects were defined as those with BP $\geq 140/90$ mmHg and/or those receiving antihypertensive medication. Subjects with fasting plasma glucose (FPG) ≥ 126 mg/dL, subjects with HbA1c $\geq 6.5\%$, and/or subjects taking oral hypoglycemic agents or receiving insulin injection were considered to be diabetic. Subjects with dyslipidemia were defined as those with LDL ≥ 140 mg/dL and/or triglycerides ≥ 150 mg/dL and/or HDL-c < 40 mg/dL and/or those taking lipid-lowering drugs. Serum UA concentration was determined by a standard analytical technique. Estimated glomerular filtration rate (eGFR) was calculated according to the following estimation formula that has been recommended by the Japan Society of Nephrology: $\text{eGFR (mL/minute/1.73}^2\text{)} = (194 \times \text{Scr}^{-1.094} \times \text{age}^{-0.287}) \times (0.739 \text{ for females}).$ ²⁰

This study was approved by the Tanushimaru branch of the Japan Medical Association and by the local mayor, as well as by the ethics committee of Kurume University School of Medicine. All of the participants gave informed consent.

Echocardiography: All individuals underwent standard M-mode and 2-dimensional echocardiography (Sono Site 180plus ultrasound system). The LV dimension was measured according to the recommendations of the American Society of Echocardiography.²¹ The LV mass (LVM) was calculated according to the formula of Devereux and Reichek:²² $\text{LVM (g)} = 1.04 [(\text{LV end-diastolic dimension (LVEDD)} + \text{end-diastolic interventricular septum thickness (IVSd)} + \text{end-diastolic LV posterior wall thickness (PWd)})^3 - (\text{LVEDD})^3] - 13.6$, where LVEDD is the end-diastolic LV internal diameter, IVSd is the ventricular septal thickness, and PWd is the posterior LV wall thickness. The LVM index (LVMI) was calculated by dividing the LVM by the body surface area. LVH was defined as $\text{LVMI} \geq 125 \text{ cm}^2$ (males), and $\text{LVMI} \geq 110 \text{ cm}^2$ (females) using the 2007 Guidelines for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC).²³ The intra- and interobserver variabilities for the measurement of LVMI were less than 5%.

Statistical analysis: Results are presented as the mean $\pm$ SD. Current smoking (no = 0 and yes = 1), and alcohol intake (no = 0 and yes = 1) were coded as dummy variables. The mean parameters stratified by tertiles of LVMI levels were compared

using analysis of variance in both sexes. To determine factors influencing serum UA and LVMI, multiple stepwise regression analysis was carried out in all subjects, and then the association was analyzed separately in males and females. The association between serum UA tertiles and LVMI in males was tested using multivariate logistic regression analysis. We calculated the unadjusted and adjusted odds ratios (ORs) of the prevalence of LVH using the lowest tertiles as the reference. In the adjusted models, we controlled factors positively associated with LVMI demonstrated by multiple regression analysis. $P < 0.05$ were considered statistically significant. All statistical analyses were performed using SAS version 9.3 (SAS Inc., Cary, NC, USA).

RESULTS

Because it is well known that UA is much higher in males than females,²⁴ and because it was so in this study (5.9 ± 1.4 mg/dL versus 4.6 ± 1.1 mg/dL; $P < 0.0001$), we separately analyzed the association in males and females (Tables I and II). Table I shows the characteristics of the 774 male subjects stratified by tertiles of LVMI. There were significant relationships between LVMI and UA in addition to age, BMI, systolic BP, medication for hypertension, triglycerides, and alcohol intake. Table II shows the characteristics of the 1,169 female subjects stratified by tertiles of LVMI. There were significant relationships between LVMI and UA in addition to age, BMI, waist circumference, systolic BP, medication for hypertension, FPG, HbA1c, medication for diabetes, prevalence of diabetes, HDL-cholesterol (inversely), triglycerides, medication for dyslipidemia, eGFR (inversely), and alcohol intake. Univariate analysis showed a significant positive correlation between LVMI and UA in both males and females (Figure).

Multivariate analysis: In males, LVMI was significantly associated with systolic BP, medication for hypertension, UA, BMI, and alcohol intake. In females, LVMI was significantly associated with age, BMI, medication for hypertension, and systolic BP. LVMI was not associated with UA in females (Table III). Accordingly, we performed a multiple logistic regression analysis only in males (Table IV). The 774 male subjects were stratified by tertiles of UA [T1: $n = 263$ (≤ 5.3 mg/dL), T2: $n = 258$ ($5.4\text{--}6.4$ mg/dL), T3: $n = 253$ (≥ 6.5 mg/dL)]. A significantly higher odds ratio of LVH (odds ratio: 1.77, 95%CI: 1.01–3.09, $P < 0.05$) was observed in the highest UA tertile versus the lowest UA tertile after adjustments for confounders.

DISCUSSION

The present study revealed a clear difference in the relationship of high serum UA and LVMI between males and females. High UA was associated with LVH only in males of a general population, independently of hypertension, obesity, and alcohol intake (Tables III and IV). Because LVH is a strong risk factor for cardiovascular events and death, our results may warrant further investigation to determine whether high UA may be a therapeutic target in males of a general population.

Among cardiovascular risk factors, LVH is one of the

Table I. Baseline Characteristics Stratified by Tertiles of LVMI in Males

Variables	LVMI level	low <i>n</i> = 261 ≤ 80	middle <i>n</i> = 261 81-103	high <i>n</i> = 252 104 ≤	<i>P</i>
Uric acid, mg/dL		5.9 ± 1.3 (1.8-9.8)	5.9 ± 1.5 (1.0-10.7)	6.2 ± 1.5 (3.1-12.4)	< 0.0001
Age, years		65.2 ± 10.6 (40-87)	65.8 ± 11.3 (40-95)	67.9 ± 10.6 (40-89)	0.014
BMI, kg/m ²		23.3 ± 3.0 (15.0-31.0)	23.8 ± 3.1 (17.0-41.0)	24.3 ± 2.9 (17.0-32.0)	0.002
Obesity, BMI ≥ 25.0 kg/m ²		90 (34.5%)	100 (38.3%)	110 (44.0%)	0.028
Waist circumference, cm		85.5 ± 8.3 (62.0-111.0)	85.7 ± 8.5 (64.0-134.0)	87.1 ± 7.9 (69.0-113.0)	0.085
Systolic BP, mmHg		131.5 ± 18.6 (88-190)	135.6 ± 17.8 (94-206)	139.4 ± 20.2 (92-208)	< 0.0001
Diastolic BP, mmHg		82.6 ± 11.0 (54-120)	84.2 ± 11.6 (50-118)	83.9 ± 11.7 (50-120)	0.207
Medication (<i>n</i> : yes) for hypertension		66 (25.5%)	93 (35.6%)	118 (47.2%)	< 0.0001
Hypertension, <i>n</i> (%)		141 (54.0%)	166 (63.6%)	181 (72.4%)	< 0.0001
FPG, mg/dL		101.7 ± 27.4 (53-280)	100.7 ± 28.7 (65-358)	101.2 ± 21.8 (70-201)	0.908
HbA1c (NGSP), %		5.9 ± 0.7 (4.8-10.1)	5.9 ± 0.7 (4.4-12.8)	6.0 ± 0.8 (4.7-12.0)	0.709
Medication (<i>n</i> : yes) for diabetes		23 (8.9%)	18 (6.9%)	29 (11.6%)	0.293
Diabetes, <i>n</i> (%)		50 (19.2%)	51 (19.5%)	54 (21.6%)	0.579
HDL-cholesterol, mg/dL		56.8 ± 13.3 (32-104)	56.3 ± 13.3 (27-102)	55.8 ± 14.4 (24-109)	0.714
LDL-cholesterol, mg/dL		120.7 ± 30.9 (26-230)	120.2 ± 29.9 (46-218)	117.7 ± 30.5 (48-212)	0.489
Triglycerides, mg/dL [†]		108.6 (40-833)	111.5 (36-849)	123.5 (33-648)	0.020
Medication (<i>n</i> : yes) for dyslipidemia		26 (10.0%)	29 (11.1%)	41 (16.4%)	0.031
Dyslipidemia, <i>n</i> (%)		116 (44.4%)	126 (48.3%)	130 (52.0%)	0.133
eGFR, mL/minute per 1.73 m ²		72.9 ± 14.6 (27.0-155.0)	73.7 ± 16.5 (8.0-123.0)	71.8 ± 18.5 (23.0-130.0)	0.405
Smoking, <i>n</i> : yes		72 (27.2%)	76 (29.1%)	51 (20.4%)	0.059
Alcohol intake, <i>n</i> : yes		182 (69.7%)	194 (74.3%)	193 (77.2%)	0.048

Data are means ± standard deviations, geometric mean, range, or percent. BMI indicates Body mass index; BP, Blood pressure; FPG, Fasting plasma glucose; and eGFR, estimated glomerular filtration rate. [†] represented as original scale after analysis by log (natural) transformed values.

most classical and strongest risk factors.²⁵⁾ Treatment of LVH decreases cardiovascular events and death.¹⁾ Thus, factors causing LVH must be investigated and treated. Consistent with previous reports, age, hypertension, and obesity were associated with LVMI in this study (Tables I and II). Because hypertension and obesity are well known factors for LVH, these may not deserve further discussion. Our finding was similar to those reported in hypertensive subjects,^{14,15)} but our study differed in that we enrolled not only hypertensive but also normotensive subjects. Because hypertension is such a strong stimulus for LVH, we further analyzed our data after excluding hypertension. Consequently, high UA was not associated with LVH (data not shown). At present, we cannot explain the negative association of high UA with LVH in normotensive subjects. One possible explanation is that the negative association could be due to the small number of normotensive subjects (*n* = 832), because the association was significant and independent of hypertension (Tables III and IV). The other explanation may be that UA levels were not so high in the enrolled normotensive subjects; the mean UA level in the highest tertile was only 7.5 ± 0.9 mg/dL. Our results indicated there was a clear difference in the relationship of UA and LVH between males and fe-

males. We were not able to clarify why there was a gender difference for the association of UA and LVH. It is possible that sex hormones may play a role. It may be interesting to note that hyperuricemia is reportedly associated with increased cardiovascular events only in males but not in females.²⁶⁾

Several studies, mainly among Caucasians, reported that serum high UA was not associated with LVH,²⁷⁻²⁹⁾ however, care should be taken in interpreting these results because most of these studies were done in somewhat obese subjects with electrocardiograms.²⁷⁾ It is well known that the diagnostic power for LVH by electrocardiograms is diminished in the presence of obesity. In this study, echocardiographically measured LVMI was apparently associated with UA, independent of obesity.

UA itself is an antioxidant,³⁰⁾ however, hyperuricemia is a risk factor for cardiovascular disease³¹⁻³³⁾ due to several mechanisms. Hyperuricemia more than 7.0 mg/dL is generally considered a cardiovascular risk in men. In the present study, we obtained a serum UA cut-off value of 6.6 mg/dL for LVH in men. It may be interesting to note that the two values are very similar.

There are several limitations to our study. First, because

Table II. Baseline Characteristics Stratified by Tertiles of LVMI in Females

Variables	LVMI level	low <i>n</i> = 397 ≤ 74	middle <i>n</i> = 375 75-94	high <i>n</i> = 397 95 ≤	<i>P</i>
Uric acid, mg/dL		4.6 ± 1.1 (0.3-8.2)	4.5 ± 1.1 (0.7-9.9)	4.8 ± 1.2 (0.7-10.7)	0.003
Age, years		63.5 ± 11.9 (40-93)	63.8 ± 11.5 (40-90)	69.1 ± 9.9 (44-90)	< 0.0001
BMI, kg/m ²		22.4 ± 3.4 (15.0-35.0)	23.0 ± 3.6 (15.0-37.0)	24.1 ± 3.5 (16.0-38.0)	< 0.0001
Obesity, BMI ≥ 25.0 kg/m ²		91 (22.3%)	110 (29.6%)	166 (41.8%)	< 0.0001
Waist circumference, cm		81.1 ± 10.3 (57.0-116.0)	82.4 ± 10.2 (56.0-113.0)	86.2 ± 10.3 (56.0-119.0)	< 0.0001
Systolic BP, mmHg		129.2 ± 18.9 (90-210)	131.0 ± 19.9 (84-212)	136.6 ± 18.7 (90-230)	< 0.0001
Diastolic BP, mmHg		79.6 ± 10.5 (50-126)	80.2 ± 10.8 (52-122)	81.3 ± 11.6 (54-136)	0.097
Medication (<i>n</i> : yes) for hypertension		86 (21.7%)	103 (27.7%)	174 (43.8%)	< 0.0001
Hypertension, <i>n</i> (%)		166 (41.8%)	189 (50.8%)	264 (66.5%)	< 0.0001
FPG, mg/dL		94.3 ± 17.4 (64-231)	96.8 ± 33.1 (71-615)	100.6 ± 26.1 (73-337)	0.003
HbA1c (NGSP), %		5.8 ± 0.5 (4.4-18.9)	5.9 ± 0.7 (3.8-14.7)	6.0 ± 0.7 (5.1-12.6)	0.021
Medication (<i>n</i> : yes) for diabetes		17 (4.3%)	18 (4.8%)	31 (7.8%)	0.032
Diabetes, <i>n</i> (%)		43 (10.8%)	45 (12.1%)	70 (17.6%)	0.005
HDL-cholesterol, mg/dL		64.5 ± 14.3 (32-121)	64.2 ± 15.6 (32-143)	61.3 ± 16.3 (24-195)	0.005
LDL-cholesterol, mg/dL		133.8 ± 33.0 (43-272)	132.8 ± 31.7 (60-233)	129.2 ± 30.1 (51-224)	0.101
Triglycerides, mg/dL [†]		96.9 (12-584)	94.6 (18-707)	104.9 (25-604)	0.014
Medication (<i>n</i> : yes) for dyslipidemia		70 (17.6%)	68 (18.3%)	94 (23.7%)	0.033
Dyslipidemia, <i>n</i> (%)		193 (48.6%)	191 (51.3%)	197 (49.6%)	0.804
eGFR, mL/minute per 1.73 m ²		73.9 ± 14.5 (24.0-122.0)	76.5 ± 15.2 (35.0-126.0)	72.8 ± 16.9 (3.0-120.0)	0.003
Smoking, <i>n</i> : yes		12 (3.0%)	18 (4.8%)	4 (1.0%)	0.092
Alcohol intake, <i>n</i> : yes		108 (27.2%)	109 (29.3%)	83 (20.9%)	0.043

Data are means ± standard deviations, geometric mean, range, or percent. BMI indicates Body mass index; BP, Blood pressure; FPG, Fasting plasma glucose; and eGFR, estimated glomerular filtration rate. [†] represented as original scale after analysis by log (natural) transformed values.

Figure. There were positive relationships between LVMI and uric acid in males and females.

of the nature of the study, the molecular mechanisms for the association of UA with LVH were not elucidated. Second, the causal relationship between UA and LVH was not clear because of the cross-sectional design of the study. Third, we did not have information on antihypertensive medications, some of which have a UA modifying (lowering or increasing) effect.

For these reasons, we are unable to say whether UA lowering drugs may be useful for treatment or prevention of LVH. Finally, the relationship of LVMI with UA was significant, but weak because the *r* value was less than 0.2. Moreover, the *P* value of UA by multiple stepwise regression analysis for LVMI shown in Table III was only 0.003, much smaller compared to *P* values of systolic blood pressure and medication for hypertension.

In summary, there was a clear difference in the relationship of UA and LVH between males and females. Hyperuricemia was significantly and independently associated with LVH evaluated by echocardiography only in males of a general population.

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Table III. Multiple Stepwise Regression Analysis for LVMI

1) Males

Variables	β	SE	P
Systolic BP, mmHg	0.300	0.050	< 0.0001
Medication (n: yes) for hypertension	9.104	2.044	< 0.0001
Uric acid, mg/dL	1.990	0.655	0.003
BMI, kg/m ²	0.763	0.324	0.019
Alcohol intake, n: yes	4.531	2.181	0.038

R² = 0.104

2) Females

Variables	β	SE	P
Age, years	0.517	0.062	< 0.0001
BMI, kg/m ²	0.315	0.198	< 0.0001
Medication (n: yes) for hypertension	5.803	1.712	0.0007
Systolic BP, mmHg	0.089	0.039	0.022

R² = 0.107

BP indicates Blood pressure; and BMI, Body mass index. [†] represented as original scale after analysis by log (natural) transformed values.

Table IV. Multiple Logistic Regression Analysis for Association Between Serum UA Levels and LVMI Evaluated by Echocardiography in Males

Models	T1	Tertiles of Uric acid T2	T3
Model 1	Ref.	1.11 (0.62-2.00)	1.93 (1.13-3.29)*
Model 2	Ref.	1.20 (0.66-2.16)	2.06 (1.20-3.54)**
Model 3	Ref.	1.16 (0.64-2.10)	1.91 (1.10-3.29)*
Model 4	Ref.	1.10 (0.60-2.00)	1.73 (0.99-3.01)
Model 5	Ref.	1.12 (0.61-2.05)	1.82 (1.04-3.18)*
Model 6	Ref.	1.11 (0.61-2.03)	1.77 (1.01-3.09)*

* indicates $P < 0.05$; and **, $P < 0.01$ versus T1. Model 1: Crude, Model 2: Adjusted for age, Model 3: Adjusted for age and medication for hypertension, Model 4: Adjusted for age, medication for hypertension and BMI, Model 5: Adjusted for age, medication for hypertension, BMI and systolic BP, Model 6: Adjusted for age, medication for hypertension, BMI, systolic BP and alcohol intake.

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