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

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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 (≤ 80 cm²: n = 261), middle (81-103 cm²: n = 261), and high (≥ 104 cm²: 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.1-3 Uric acid (UA) may induce LVH and the following mechanisms have been proposed.4-6 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.11-13 However, the results have not been consistent. Some studies reported a positive association only in males14,15 and others reported such an association only in females.14 In some studies,11,13,15 the enrolled subjects were only hypertensive while in others,12,13 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,14,15 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
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. 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 ≥ 140/90 mmHg and/or those receiving antihypertensive medication. Subjects with fasting plasma glucose (FPG) ≥ 126 mg/dL, subjects with HbA1c ≥ 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 measured by a standard enzymatic technique. Estimated glomerular filtration rate (eGFR) was calculated according to the following estimation formula that has been recommended by the Japanese Society of Nephrology: eGFR (mL/minute/1.73²) = (194 × Scr⁻¹.094 × age⁻⁰.287) × (0.739 for females).

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. The LV mass (LVM) was calculated according to the formula of Devereux and Reichek: LVM (g) = 1.04 [(LV end-diastolic dimension (LVEDD) + end-diastolic interventricular septum thickness (IVSd) + end-diastolic LV posterior wall thickness (PWd)]³ – (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 LVMI ≥ 125 cm² (males), and LVMI ≥ 110 cm² (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). The intra- and interobserver variabilities for the measurement of LVMI were less than 5%.

**Statistical analysis:** Results are presented as the mean ± 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, 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, 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 (5.4-6.4 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
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,¹⁴,³⁵ 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 hypertensive subjects. Because hypertension is such a strong stimulus for LVH, we excluded hypertensive subjects.

Several studies, mainly among Caucasians, reported that serum high UA was not associated with LVH,¹²⁻²⁰ however, care should be taken in interpreting these results because most of these studies were done in somewhat obese subjects with electrocardiograms.²⁶ 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 disease.¹¹⁻¹³ 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, independent of obesity. It may be interesting to note that the two values are very similar.

There are several limitations to our study. First, because...
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.

Acknowledgment

We are grateful to the members of the Japan Medical Association of Ukiha, the elected officials and residents of Tanushimaru, and the team of cooperating physicians for their help in performing the health examinations.
Table III. Multiple Stepwise Regression Analysis for LVMI

1) Males

<table>
<thead>
<tr>
<th>Variables</th>
<th>β</th>
<th>SE</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Systolic BP, mmHg</td>
<td>0.300</td>
<td>0.050</td>
<td>&lt;0.0001</td>
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<tr>
<td>Medication (n: yes) for hypertension</td>
<td>9.104</td>
<td>2.044</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>1.990</td>
<td>0.655</td>
<td>0.003</td>
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<tr>
<td>BMI, kg/m²</td>
<td>0.763</td>
<td>0.324</td>
<td>0.019</td>
</tr>
<tr>
<td>Alcohol intake, n: yes</td>
<td>4.531</td>
<td>2.181</td>
<td>0.038</td>
</tr>
</tbody>
</table>

R² = 0.104

2) Females

<table>
<thead>
<tr>
<th>Variables</th>
<th>β</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>0.517</td>
<td>0.062</td>
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<tr>
<td>BMI, kg/m²</td>
<td>0.315</td>
<td>0.198</td>
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<td>Medication (n: yes) for hypertension</td>
<td>5.803</td>
<td>1.712</td>
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<tr>
<td>Systolic BP, mmHg</td>
<td>0.089</td>
<td>0.039</td>
<td>0.022</td>
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</table>

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

<table>
<thead>
<tr>
<th>Models</th>
<th>Tertiles of Uric acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
</tr>
<tr>
<td>Model 1 (Ref.)</td>
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<tr>
<td>Model 2</td>
<td>1.20 (0.66-2.16)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.16 (0.64-2.10)</td>
</tr>
<tr>
<td>Model 4</td>
<td>1.10 (0.60-2.00)</td>
</tr>
<tr>
<td>Model 5</td>
<td>1.12 (0.61-2.05)</td>
</tr>
<tr>
<td>Model 6</td>
<td>1.11 (0.61-2.03)</td>
</tr>
</tbody>
</table>

* 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.

REFERENCES


12. Kurata A, Shigematsu Y, Higaki J. Sex-related differences in relations of uric acid to left ventricular hypertrophy and remodeling in...


