Circ J 2006; **70:** 885–888

Gender-Related Association of Serum Uric Acid and Left Ventricular Hypertrophy in Hypertension

Kiyoshi Matsumura, MD; Toshio Ohtsubo, MD; Hideyuki Oniki, MD;
Koji Fujii, MD; Mitsuo Iida, MD

Background The aim of the present study was to determine whether sex differences contribute to the association of serum uric acid and left ventricular hypertrophy in individuals with hypertension.
Methods and Results Seventy participants with essential hypertension (34 men, 36 women; 54.4±1.6 years old) were enrolled to undergo echocardiography to calculate the left ventricular mass index (LVMI). Twenty-four-hour ambulatory blood pressure monitoring was done to assess blood pressure level precisely. The LVMI was significantly correlated with serum uric acid (r=0.295, p=0.013) in all participants. After controlling for factors such as age, sex, mean 24-h systolic blood pressure, creatinine clearance, and duration of hypertension, serum uric acid was still found to be significantly and independently associated with LVMI. Because serum uric acid was significantly higher in men than in women (6.8±0.3 and 5.1±0.2 mg/dl, respectively), subsequent analysis was performed by gender. Multiple regression analysis revealed that the LVMI was significantly and independently associated with serum uric acid in women, but not in men.
Conclusions The potential effect of uric acid on LV hypertrophy is more pronounced in female than in males with essential hypertension. (*Circ J* 2006; **70:** 885–888)

Key Words: Gender; Hypertension; Left ventricular hypertrophy; Uric acid

Several epidemiological studies have shown that associations between increased serum uric acid and cardiovascular risk are present not only in the general population, but also in patients with hypertension,[1–4] although the underlying mechanisms for these associations are not well understood.[5] Left ventricular (LV) hypertrophy, which is likely to be involved in cardiovascular disease,[6] is the most common cardiac complication caused by hypertension; however, the role of serum uric acid on the progression of LV hypertrophy in inidviduals with hypertension has not been well characterized.[7]

The individuals participating in the Losartan Intervention For Endpoint reduction in hypertension study had clinical characteristics of hypertension with electrocardiographic signs of LV hypertrophy,[8] and this study indicated that the association between serum uric acid and cardiovascular events was stronger in women than in men with or without adjustment of Framingham risk score.[9] In contrast, another study reported an association between serum uric acid and LV hypertrophy in men, but not in Japanese hypertensive individuals women.[10] The association of serum uric acid and LV hypertrophy might thus be dependent on sex, although previous studies have reported divergent results in this regard.[9,10] We anticipated that these divergent findings might be attributable to the difficulty of precisely assessing blood pressure in these indiviuals, because casual blood pressures are easily influenced by physical activities.

(Received March 17, 2006; revised manuscript received April 24, 2006; accepted May 1, 2006)
Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
Mailing address: Kiyoshi Matsumura, MD, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. E-mail: matsumk@intmed2.med.kyushu-u.ac.jp

Accordingly, the aim of the present study was to determine whether sex differences still contribute to the association of serum uric acid and LV hypertrophy in subjects with hypertension, even after considering the individuals' own blood pressure. To keep the blood pressure levels adjusted correctly, all individuals were admitted to the hospital and 24-h ambulatory blood pressure monitoring was conducted.

Methods

Participants

The study group consisted of 70 essential hypertensive patients admitted to the Kyushu University Hospital in Fukuoka, Japan. All possible causes of secondary hypertension had been excluded, all patients were in sinus rhythm, and none had any valvular or ischemic heart disease. None of the patients was receiving any antihypertensive or antihyperuricemic agents. The details of the study protocol were explained to the individuals, and their informed consent was obtained before participation.

Physical and Laboratory Examinations

The 24-h non-invasive ambulatory blood pressure monitoring was performed using an ABPM-630 (Nippon Colin Co, Komaki, Japan) or TM-2421 (A&D Co Inc, Tokyo, Japan). A cuff-oscillometric method was used, and the measurement interval was set at 20 min. Height and weight were measured, and the body mass index (BMI) was calculated. The BMI was defined as the weight (in kg) divided by the height (m^2). Serum uric acid and creatinine concentrations were determined by a standard analytical technique. Creatinine clearance (Ccr) was calculated according to the Cockcroft-Gault equation:[11] Ccr (ml/min) = [(140 − age × weight)/(72 × serum creatinine)] × (0.85 for females).

Table 1 Clinical Characteristics of the Subjects With Essential Hypertension

Variables	All	Men	Women
n	70	34	36
Age (years)	54.4±1.6	53.3±2.6	55.4±2.0
BMI (kg/m^2)	22.8±0.3	23.3±0.4	22.4±0.5
Duration of hypertension (years)	10.8±1.2	12.6±1.9	9.2±1.4
Mean 24-h SBP (mmHg)	136.6±1.8	135.9±2.7	137.4±2.5
Mean 24-h DBP (mmHg)	80.6±1.2	81.3±1.6	79.9±1.8
Mean 24-h PR (/min)	68.1±0.9	65.7±1.3*	70.3±1.2
Serum creatinine (μmol/L)	74.3±2.0	82.9±2.7**	66.2±2.2
Ccr (ml/min)	79.7±3.1	87.0±5.1*	72.9±3.4
Serum uric acid (μmol/L)	350.5±12.3	401.7±16.0**	302.2±14.5
Proteinuria (%)	11.4	17.6	5.6
Keith-Wagener ≥IIa (%)	31.4	26.5	36.1

Values are mean±SE.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; Ccr, creatinine clearance.
**p<0.05, **p<0.01 vs women.*

Table 2 Echocardiographic Characteristics of the Subjects With Essential Hypertension

Variables	All	Men	Women
n	70	34	36
LVEDD (mm)	46.0±0.5	46.8±0.6	45.3±0.9
LVESD (mm)	27.4±0.6	28.0±0.6	26.9±1.0
IVSd (mm)	10.3±0.2	11.1±0.3**	9.5±0.3
PWd (mm)	10.0±0.2	10.6±0.3**	9.4±0.3
RWT	0.444±0.011	0.464±0.013	0.425±0.017
LVM (g)	190.6±6.5	215.9±8.9**	166.7±7.5
LVM index (g/m^2)	118.9±3.6	125.7±4.7	112.4±5.2
LAD (mm)	33.9±0.7	34.2±0.8	33.5±1.2
AoD (mm)	29.8±0.5	31.8±0.7	27.9±0.5
FS (%)	40.5±1.0	40.1±1.2	40.9±1.5
EF (%)	71.5±1.0	71.6±1.6	71.3±1.4
CO (l/min)	4.6±0.1	4.6±0.2	4.6±0.2

Values are mean±SE.
LVEDD, left ventricular (LV) end-diastolic dimension; LVESD, LV end-systolic dimension; IVSd, end-diastolic interventricular septum thickness; PWd, end-diastolic LV posterior wall thickness; RWT, relative wall thickness; LVM, LV mass; LAD, left atrial dimension; AoD, aortic root diameter; FS, fractional shortening; EF, ejection fraction; CO, cardiac output.
***p<0.01 vs women.*

Echocardiography

All individuals underwent standard M-mode and 2-dimensional echocardiography (SSH-160A; Toshiba Co, Tokyo, Japan) with a 3.5-MHz transducer. The LV dimension was measured according to the recommendations of the American Society of Echocardiography![12] The LV mass (LVM) was calculated according to the formula of Devereux and Reichek:[13] 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. The relative wall thickness (RWT) was calculated at end-diastole according to the following equation: RWT=(interventricular septum thickness+posterior wall thickness)/LV diameter. The LV volume was calculated by Teichholz's formula![14] and an ejection fraction (EF) was obtained by the conventional method.

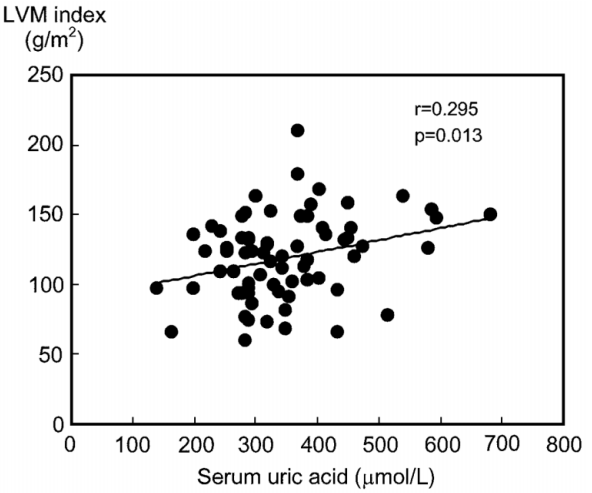

Fig 1. Scatterplots showing the relationship between serum uric acid and left ventricular mass (LVM) index in all individuals.

Table 3 Multiple Regression Analysis for Left Ventricular Mass Index

Independent variables	β	p value
Creatinine clearance (ml/min)	0.638	0.008
Age (years)	1.267	0.004
Mean 24-h SBP (mmHg)	0.551	0.016
Serum uric acid (μmol/L)	0.096	0.033
Habitual alcohol intake	13.623	0.11
BMI (kg/m^2)	–2.416	0.15
Blood glucose (mmol/L)	2.866	0.24
Sex (men/women: 0/1)	8.044	0.38
Duration of hypertension (years)	0.019	0.96

β, *regression coefficient. Other abbreviations see in Table 1.*

Table 4 Multiple Regression Analysis for Left Ventricular Mass Index in Men and Women

Independent variables	Men		Women	
	β	p value	β	p value
Creatinine clearance (ml/min)	0.417	0.13	0.575	0.17
Age (years)	0.232	0.66	1.955	0.007
Mean 24-h SBP (mmHg)	0.886	0.005	0.161	0.65
Serum uric acid (μmol/L)	0.069	0.29	0.159	0.027
Habitual alcohol intake	15.618	0.13	18.451	0.19
BMI (kg/m^2)	–0.535	0.86	–2.449	0.24
Blood glucose (mmol/L)	4.147	0.20	2.478	0.53
Duration of hypertension (years)	0.547	0.20	–0.602	0.34

Abbreviations see in Tables1,3.

Data Analysis

The data are expressed as the mean±SE. Comparisons between men and women were performed by Student's t-test. To determine the factors influencing the LVMI, multiple regression analysis was carried out. The p-values <0.05 were considered statistically significant.

Results

Table 1 summarizes the clinical characteristics of the individuals. The mean 24-h systolic and diastolic blood pressures were comparable between men and women. In contrast, serum uric acid was significantly higher in men

than in women. The results of the measurements of LV wall thickness and dimensions as determined by echocardiography are presented in Table 2. The end-diastolic interventricular septum and LV posterior wall thicknesses were greater in men than in women; however, the end-systolic and end-diastolic LV diameters, LVMI, and EF did not differ between the sexes.

The LVMI significantly correlated with serum uric acid concentration in all subjects (r=0.295, p=0.013; n=70) (Fig 1). In multiple regression analysis, after controlling for age, sex, BMI, mean 24-h systolic blood pressure, Ccr, blood glucose, alcohol intake, and duration of hypertension, serum uric acid concentration was still found to be significantly and independently associated with LVMI in all individuals (Table 3).

Because serum uric acid was significantly higher in men than in women (Table 1), further analysis was calculated according to sex. The LVMI was significantly correlated with serum uric acid concentration in women (r=0.349, p=0.037; n=36), but not in men (r=0.072, p=0.68; n=34). Furthermore, multiple regression analysis also revealed that the LVMI was significantly and independently associated with serum uric acid concentration in women, but not in men (Table 4).

Discussion

In the present study, serum uric acid was positively correlated with LVMI in all hypertensive individuals. Furthermore, after controlling for age, sex, BMI, mean 24-h systolic blood pressure, Ccr, blood glucose, alcohol intake, and duration of hypertension, serum uric acid was still found to be significantly and independently associated with LVMI in women, but not in men. These findings suggest that sex differences played some role in the association of serum uric acid and LV hypertrophy in the present study.

LV hypertrophy, which is likely to be related to cardiovascular disease or cardiovascular morbidity[6] is the most common cardiac complication caused by hypertension. It has been shown that total myocardial interstitial purine metabolites are increased in the failing heart of rats with post-myocardial infarction LV remodeling;[15] however, little information is available regarding the association between serum uric acid and LV hypertrophy in humans. There are conflicting results regarding the effects of uric acid on cardiovascular disease or LV hypertrophy in each gender; however, most studies have reported that the association of serum uric acid and cardiovascular mortality or hypertensive target organ damage is more pronounced in women than in men[2,7,16] The present study supports these previous findings: serum uric acid was clearly associated with LV hypertrophy in females, but not males, with essential hypertension.

All of the present participants were examined after admission to hospital, and blood pressure was assessed by using 24-h ambulatory monitoring, not by casual meaasurement. It has been shown that ambulatory blood pressure monitoring is better then casual measurements for predicting LV hypertrophy and cardiovascular complications[17,18] Therefore, it is expected that the blood pressure adjustments made in the present patients would be more useful for predicting LV hypertrophy than adjustments based on casual blood pressure monitoring. As a result, the present study is the first to use 24-h ambulatory blood pressure monitoring to show the role of sex in the association between serum uric acid and LV hypertrophy. In contrast, Kurata et al reported the opposite association; that is, an association between serum uric acid and concentric LV hypertrophy in men, but not in women[10] It is difficult to account for this difference in results, but it seems possible that they were caused by methodological difference in blood pressure measurements (ie, ambulatory blood pressure monitoring vs casual measurements).

The present study did not clarify the mechanisms linking uric acid and LV hypertrophy, although hyperuricemia has previously been shown to predict stroke and the development of hypertension and renal disease[5,7,9,19,20] The role of uric acid in cardiovascular complications has not been established; however, some potential mechanisms have been proposed: proliferation of vascular smooth muscle cells;[21] stimulation of the inflammatory pathway;[22] and prothrombotic effects mediated by platelet activation[23] Furthermore, it has also been shown that inhibition of xanthine oxidase with allopurinol, which is the usual treatment of hyperuricemia, improves endothelial dysfunction in subjects with type 2 diabetes and coexisting mild hypertension[24] These previous findings suggest that oxidative stress might be a factor accounting for the results of the present study. Furthermore, sex hormones might also interact with serum uric acid or LV hypertrophy. Further studies are necessary to determine the relationships among uric acid, LV hypertrophy, oxidative stress, and sex hormones.

The effect of treatment to decrease serum uric acid on LV hypertrophy or remodeling was not investigated. It has been shown that serum uric acid is independently associated with LVM and that the combination of hyperuricemia and LV hypertrophy is an independent and powerful predictor for cardiovascular disease in patients with essential hypertension[25] In the present study, the association between serum uric acid and LVM was more pronounced in the women with essential hypertension than in the men. Therefore, treatment with allopurinol, which inhibits xanthine oxidase and decreases serum uric acid, might have some beneficial effects on the prevention of LV hypertrophy or cardiovascular complications, especially in women. Prospective clinical trials to determine the effects of reduction of serum uric acid on cardiovascular diseases will be needed to clarify the precise role of uric acid in cardiovascular systems.

In conclusion, in the present study serum uric acid was associated with LV hypertrophy in women with essential hypertension, but not in the male subjects. Oxidative stress or sex hormones might account for this association, although the underlying mechanisms were not been determined in the present study. Adequate control of serum uric acid might prevent the progression of LV hypertrophy, especially in women with essential hypertension. Further studies are necessary to determine whether treatment of hyperuricemia improves or prevents LV hypertrophy in patients with essential hypertension.

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