Original Article

Sex-Related Differences in Relations of Uric Acid to Left Ventricular Hypertrophy and Remodeling in Japanese Hypertensive Patients

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Both hyperuricemia and echocardiographically determined left ventricular (LV) mass have a well-determined association with cardiovascular morbidity and mortality. However, whether or not there is a sex difference in the association of serum uric acid level with LV mass has never been systematically explored. We examined the sex-specific relation of serum uric acid level and echocardiographic indexes of LV structure in never-treated patients with essential hypertension. We enrolled 160 never-treated hypertensive patients (89 men and 71 women) to assess the possible relationship between LV mass and serum uric acid levels. LV measurements were performed according to the recommendations of the American Society of Echocardiography and the Penn Convention. LV mass was indexed by height, body surface area and height raised to the 2.7th power. A positive significant correlation between LV geometry (LV mass, indexed LV mass and relative wall thickness) and serum uric acid level was found in male hypertensive patients but not in female hypertensive patients. Independent determinants of serum uric acid levels in male hypertensive patients were LV mass and serum creatinine levels. In addition, male hypertensive patients with concentric hypertrophy showed the highest serum uric acid levels. In comparison, independent determinants of serum uric acid levels in female hypertensive patients were age and serum creatinine levels. In conclusion, these findings indicate a sex difference in the association of uric acid with LV geometry in Japanese hypertensive patients. In addition, the finding that the highest levels of serum uric acid were observed in our male hypertensive patients with concentric hypertrophy confirmed the previous reports that these patients have the highest risk for cardiovascular morbidity and mortality. (*Hypertens Res* 2005; 28: 133–139)

***Key Words*: essential hypertension, serum uric acid, left ventricular mass, concentric hypertrophy**

Introduction

Many epidemiological studies have suggested that serum uric acid is a risk factor for cardiovascular disease (*1*–*7*). Elevated serum uric acid levels are accompanied by obesity, dyslipidemia, hypertension and insulin resistance, and all of which are also associated with increased risk for cardiovascular disease (*8*). The Chicago Industry Heart Study (*4*), a prospective 11.5-year study of 2,400 industrial workers, found serum uric acid levels to be independently associated with increased cardiovascular morbidity and mortality, but only in women. In Japan, there is a report suggesting a significant correlation between elevated serum uric acid levels and cardiovascular risk factors in large members of men, but not women (*5*). While sex-related differences in the impact of elevated serum uric acid levels on future cardiovascular disease have been reported, the sex-related specific role of serum uric acid in relation to cardiovascular disease has been unclear.

Echocardiographically determined left ventricular (LV) hypertrophy is known to be a powerful, independent risk factor of future cardiovascular morbidity and mortality in

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Received September 21, 2004; Accepted in revised form November 17, 2004.

Table 1. Hemodynamic and Echocardiographic Characteristics in Study Subjects

Characteristic	Normotensive control subjects (n=64)	Hypertensive patients (n=160)	p values
Age (years)	55±10	58±11	ns
Male/female	39/25	89/71	
Heart rate (beats/min)	65±9	69±9	ns
Blood pressure (mmHg)			
Systole	121±12	169±18	<0.0001
Diastole	71±10	95±14	<0.0001
Pulse pressure (mmHg)	50±11	74±18	<0.0001
LV mass/BSA (g/m^2)	82.5±19.0	116.3±29.5	<0.0001
Relative wall thickness	0.32±0.06	0.40±0.07	<0.0001
Doppler stroke volume (ml)	82.8±13.4	81.6±13.7	ns
Percent fractional shortening (%)	39.9±5.5	36.3±5.8	<0.0001

Data are presented as the mean±SD. LV, left ventricular; BSA, body surface area; ns, not significant.

patients with uncomplicated essential hypertension as well as the general population (*9–12*). Furthermore, there is increasing evidence of a link between LV hypertrophy and hypertensive target organ damage (*13–15*). An association of increased LV mass with adverse outcomes has been consistently reported in men and women, but the question of whether or not the relative strength of the relation of serum uric acid level to LV mass is similar in the two sexes has never been systematically explored. Accordingly, we examined the sex-specific relation of serum uric acid level and echocardiographic indexes of LV structure in never-treated patients with essential hypertension.

Methods

Study Population

One hundred and sixty never-treated patients (89 men and 71 women) with uncomplicated essential hypertension were enrolled in the study. Patients were excluded who had a pre-existing cardiac disease, a pre-existing medical illness, such as diabetes mellitus, or M-mode echocardiograms inadequate for clearly detecting the internal lines of the interventricular septum and LV posterior wall. Sixty-four age- and sex-matched normotensive subjects (35 men and 29 women) who had no history of hypertension and no evidence of cardiac disease served as controls. All study subjects participated in this study after giving informed consent. The study was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

Physical Examinations

Weight and height were measured while the subjects were fasting overnight and wearing only underwear. Body mass index (BMI) was calculated as weight (kg) divided by [height (m)]^2. Blood pressure was measured in triplicate by a single physician who was expert in the evaluation of hypertension, with an appropriate arm cuff and a mercury sphygmomanometer after 5 min of rest in the sitting position. The arithmetic mean of the last two measurements was calculated. Korotkoff phase V was taken for diastolic blood pressure. Hypertension was defined as a blood pressure above 140/90 mmHg, according to the classification of BP for adults in the Guideline for the Management of Hypertension for General Practitioners (JSH 2000) (*16*).

Biochemical Measurements

In the morning, after an overnight fast, venous blood was sampled for the measurement of serum uric acid, serum creatinine, and serum concentrations of total cholesterol (TC), high density lipoprotein (HDL) cholesterol and triglycerides (TG). Uric acid was analyzed by the uricase-peroxidase method. Normal serum uric acid levels in our laboratory are 4.3–8.0 mg/dl for men, and 2.7–5.8 mg/dl for women. Creatinine was analyzed by Jaffe's method (normal range in our laboratory: 0.5–1.2 mg/dl). The 24-h urine collections for creatinine clearance in hypertensive patients were supervised by the nursing staff. The 24-h creatinine clearance was taken as an index of glomerular filtration rate. Measurements of serum creatinine, urinary creatinine, serum uric acid, TC, HDL cholesterol and TG were carried out using an automatic analyzer (model TBA-60S; Toshiba Inc., Tokyo, Japan).

Echocardiographic Measurements

Two-dimensionally guided M-mode echocardiography was performed by standard methods, as previously outlined (*17*) using an SSD-870 or SSD-5500 echocardiograph with a 3.5 MHz transducer (Aloka Inc., Tokyo, Japan). LV internal dimension (LVID) and interventricular septal thickness (IVST) and posterior wall thickness (PWT) were measured at end-diastole and end-systole, according to the American

Table 2. Sex-Related Differences in Hemodynamic and Echocardiographic Characteristics in Hypertensive Patients

Characteristic	Male hypertensive patients (n=89)	Female hypertensive patients (n=71)	p values
Age (years)	57±11	60±11	ns
Heart rate (beats/min)	70±9	68±8	ns
Blood pressure (mmHg)			
Systole	168±18	169±17	ns
Diastole	97±16	92±12	ns
Pulse pressure (mmHg)	73±19	77±15	ns
LV mass/ BSA (g/m^2)	120.5±30.6	111.2±27.4	0.0459
Relative wall thickness	0.41±0.07	0.39±0.07	ns
Doppler stroke volume (ml)	81.5±14.1	80.6±12.6	ns
Percent fractional shortening (%)	35.0±5.9	37.9±5.4	0.0014

Data are presented as the mean±SD. LV, left ventricular; BSA, body surface area; ns, not significant.

Society of Echocardiography guidelines (*18*), and used for all purposes except determination of LV mass. LV mass was calculated at end-diastole by using the Penn convention (*19*). LV mass/height, LV mass/body surface area (BSA) and LV mass/height$^{2.7}$ were calculated as indexed LV mass. Relative wall thickness (RWT) was calculated as 2×(PWTd/LVIDd), where d is end-diastole. Percent fractional shortening (FS) was calculated as (LVIDd − LVIDs)/LVIDd × 100 and was used as an indicator of LV systolic function, where d and s are end-diastole and end-systole, respectively. Aortic annular cross-sectional area (in cm^2) was calculated from the measured aortic annulus and multiplied by the aortic time-velocity integral in cm to yield Doppler stroke volume (SV) (*20*).

Subgroups Analysis

On the basis of the relationship between RWT and LV mass/BSA, 89 male and 71 female hypertensive patients were then divided into 4 different groups, respectively. The partition values of 0.44 for RWT and 108 g/m^2 (male) or 104 g/m^2 (female) for LV mass/BSA, the mean+2SD value of normotensive control subjects, were used. The groups consisted of male hypertensive patients with normal RWT and LV mass/BSA (normal geometry; n=31, 35%); patients with concentric remodeling (n=5, 6%); patients with concentric hypertrophy (n=22, 24%); and patients with eccentric hypertrophy (n=31, 35%). Furthermore, the groups consisted of female hypertensive patients with normal RWT and LV mass/BSA (normal geometry; n=27, 38%); patients with concentric remodeling (n=5, 7%); patients with concentric hypertrophy (n=12, 17%); and patients with eccentric hypertrophy (n=27, 38%).

Statistical Analysis

All values are expressed as the mean±SD. Two tailed unpaired Student's t-test was used to compare study response variables between categories. Correlation coefficients were calculated according to Pearson's method. A multiple regression analysis was also performed to select appropriate independent variables producing the highest partial correlation with serum uric acid level in patients with hypertension. Probability values <0.05 were considered statistically significant in all analyses.

Results

Hemodynamic and Echocardiographic Characteristics

Office systolic blood pressure, diastolic blood pressure or pulse pressure was significantly higher in hypertensive patients than that in normotensive control subjects. LV mass/BSA and RWT were also larger in hypertensive patients than those in normotensive control subjects. Although Doppler stroke volume did not differ significantly, percent fractional shortening in hypertensive patients was lower than that in normotensive control subjects (Table 1).

Sex-Related Differences in Hemodynamic and Echocardiographic Characteristics

There were no significant differences in age, heart rate, systolic blood pressure, diastolic blood pressure and pulse pressure between male and female hypertensive patients. Although LV mass/BSA in male hypertensive patients was larger than that in female hypertensive patients, RWT and Doppler stroke volume did not differ significantly. Furthermore, percent fractional shortening in female hypertensive patients was higher than that in male hypertensive patients (Table 2).

Sex-Related Differences in Biochemical Characteristics

Although there was no significant difference in the 24-h crea

Table 3. Sex-Related Differences in Biochemical Characteristics in Hypertensive Patients

Characteristic	Male hypertensive patients (n=89)	Female hypertensive patients (n=71)	p values
Serum uric acid (mg/dl)	6.75±1.39	5.46±1.07	<0.0001
Serum creatinine (mg/dl)	0.99±0.31	0.75±0.20	<0.0001
Creatinine clearance (ml/min)	84.5±28.1	91.9±24.2	ns
Body mass index (g/m^2)	24.1±2.3	24.5±3.9	ns
Total cholesterol (mg/dl)	199±39	217±40	0.0055
HDL cholesterol (mg/dl)	40±12	47±14	0.0031
Triglyceride (mg/dl)	139±61	118±36	ns

Data are presented as the mean±SD. HDL, high density lipoprotein; ns, not significant.

Table 4. Simple Correlation of Serum Uric Acid Level with Age, Left Ventricular Geometry and Function in Male and Female Patients with Hypertension

Variable	Serum uric acid level			
	Male HT (n=89)		Female HT (n=71)	
	r values	p values	r values	p values
Age	0.037	0.7310	0.307	0.0092
LV mass	0.399	0.0001	0.134	0.2646
LV mass/height	0.353	0.0007	0.150	0.2115
LV mass/BSA	0.371	0.0004	0.151	0.2086
LV mass/height$^{2.7}$	0.355	0.0006	0.174	0.1458
RWT	0.324	0.0019	0.018	0.8848
Percent FS	0.038	0.7268	0.080	0.5061

HT, hypertension; LV, left ventricular; BSA, body surface area; RWT, relative wall thickness; FS, fractional shortening.

tinine clearance between male and female hypertensive patients, serum uric acid and serum creatinine levels in male hypertensive patients were significantly higher than those in female hypertensive patients. Both total and HDL cholesterol levels in female hypertensive patients were significantly higher than those in male hypertensive patients. There were no significant differences in BMI and TG levels between the male and female hypertensive groups (Table 3).

Correlations between Serum Uric Acid Levels and LV Geometry or Serum Lipid Levels

As shown in Table 4, serum uric acid levels were significantly related to LV mass, LV mass/height, LV mass/BSA, LV mass/height$^{2.7}$ and RWT in male hypertensive patients. However, serum uric acid levels were not significantly related to LV geometry (LV mass, indexed LV mass and RWT) in female hypertensive patients. Serum uric acid levels were not significantly related to percent FS in either male or female hypertensive patients. Furthermore, serum uric acid levels were not significantly related to BMI, TC, HDL cholesterol or TG levels in either male or female hypertensive patients. Table 5 shows the results of multiple regression analysis. Independent determinants of serum uric acid levels in male hypertensive patients were LV mass and serum creatinine levels. In contrast, independent determinants of serum uric acid levels in female hypertensive patients were age and serum creatinine levels. In addition, Fig. 1A shows the comparison of serum uric acid levels in male hypertensive patients with normal geometry (6.1±1.1 mg/dl), concentric remodeling (6.9±1.6 mg/dl), concentric hypertrophy (7.5±1.2 mg/dl) and eccentric hypertrophy (6.8±1.5 mg/dl). Male hypertensive patients with concentric hypertrophy showed the highest serum uric acid levels. However, there were no significant correlations between serum uric acid levels and LV geometry in female hypertensive patients. Figure 1B shows the comparison of serum uric acid levels in female hypertensive patients with normal geometry (5.1±0.9 mg/dl), concentric remodeling (5.7 ± 1.3 mg/dl), concentric hypertrophy (5.2±1.2 mg/dl) and eccentric hypertrophy (5.8±1.1 mg/dl).

Discussion

In this cross-sectional study, serum uric acid levels correlated positively with LV geometry (LV mass, indexed LV mass and RWT) in male hypertensive patients, but not in female hypertensive patients. In comparison, serum uric acid levels correlated positively with age in female hypertensive patients, but not in male hypertensive patients. These findings indicate a sex difference in the association of uric acid with LV geome-

Table 5. Multiple Regression Analysis of Factors Relevant to Serum Uric Acid Level in Male and Female Patients with Hypertension

Variable	Serum uric acid level					
	Male HT (n=89)			Female HT (n=71)		
	β	t values	p values	β	t values	p values
Age	−0.075	−0.729	0.4682	0.422	3.109	0.0028
Body mass index	0.012	0.123	0.9027	0.184	1.564	0.1226
LV mass	0.359	3.567	0.0006	0.059	0.487	0.6279
Serum creatinine	0.316	3.181	0.0021	0.306	2.478	0.0159
Systolic BP	−0.007	−0.065	0.9481	−0.017	−0.133	0.8947
Diastolic BP	−0.132	−1.190	0.2373	0.029	0.189	0.8507
	Multiple R^2 =0.213, p=0.0003			Multiple R^2 =0.258, p=0.0151		

HT, hypertension; LV, left ventricular; BP, blood pressure.

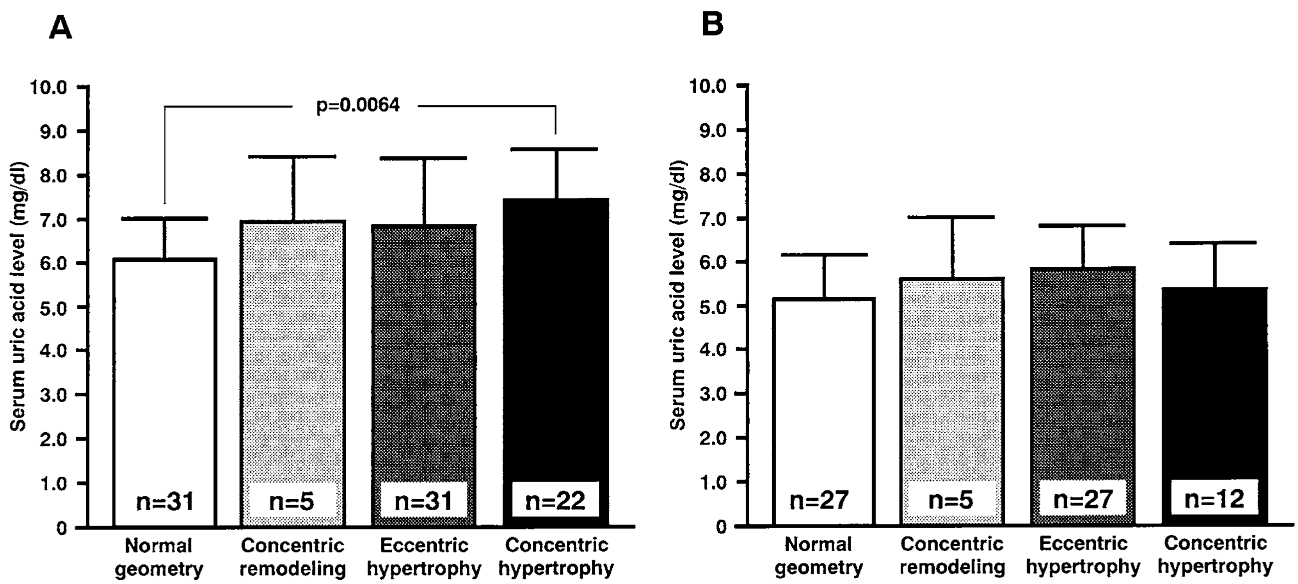

Fig. 1. *Comparison of the serum uric acid levels in male (A) and female (B) hypertensive patients with normal geometry, concentric remodeling, concentric hypertrophy and eccentric hypertrophy. Column height represents the mean; bars indicate 95% confidence intervals.*

try in Japanese hypertensive patients.

At least two prior investigations that performed sex-specific analyses reported an association of hyperuricemia with increased cardiovascular morbidity and mortality in women but not men (*4*, *21*). In contrast, one previous report has suggested a significant correlation between hyperuricemia and cardiovascular risk factors in large members of men, but not women in Japan (*5*). Furthermore, it is well recognized that increased LV mass is an independent predictor for cardiovascular morbidity and mortality in both men and women. Our results provide the first evidence that serum uric acid levels in male hypertensive patients are positively correlated with echocardiographic LV mass but not in female hypertensive patients. The present data also demonstrate that when we classify male hypertensive patients on the basis of their pattern of LV geometry, the highest serum uric acid levels are evident in patients with concentric hypertrophy.

Our clinical study design did not enable us to clearly state why serum uric acid levels are correlated with LV mass only in male hypertensive patients. However, our data are consistent with Japanese epidemiological evidence that hyperuricemia may be associated with increased cardiovascular events in men, but not in women (*5*). Thus, our findings add further support to the concept that serum uric acid level is a sensitive indicator of the future cardiovascular events in Japanese male patients with hypertension. However, it should be emphasized that the serum uric acid levels reported in this study were derived from fasting blood. It is well recognized that serum uric acid levels in humans have circadian rhythm. Elevated serum uric acid levels accentuate after ingestion of a high-protein meal or alcohol intake, but not after a low-protein meal. Thus, fasting levels may not adequately reflect the effect of uric acid on coronary circulation.

Different indexes of LV mass have been proposed for normalization of mass for body size (*9*, *22*, *23*). The optimal index, if a generalizable one exists, is still undefined, and the use of differing indexes in the literature can cause confusion. In the present study, the use of 3 different indexes of LV mass, which were normalized LV mass for body size resulted in no significant differences in the major findings.

Age was an independent predictor for the elevation of serum uric acid level in female hypertensive patients. The relation between age and the occurrence of hyperuricemia differed between men and women. Hyperuricemia correlated negatively with age in men but positively with age in women (*5*, *24*, *25*). In our study, a positive correlation between serum uric acid level and age was also recognized in female hypertensive patients. Interactions of sex hormones have been suggested as a possible cause of the difference in correlation between serum uric acid level and age in men and women (*4*). Furthermore, the LV wall thickness and LV mass have been shown to significantly increase with advancing age in healthy normotensive subjects (*26*, *27*). Therefore, the absence of an association between serum uric acid level and LV mass in female hypertensive patients in the present study may have been due to the small sample size.

In the early stage of hypertension, the serum uric acid level increases as renal blood flow decreases without affecting the glomerular filtration rate (*28*). Therefore, it certainly is possible that uric acid may be an earlier and more sensitive marker of decreased renal blood flow than serum creatinine. Furthermore, there is increasing evidence that hyperuricemia is associated with a multimetabolic syndrome (*29*) in which insulin-mediated renal hemodynamic abnormalities lead to hypertensive renal damage (*30*, *31*). Facchini *et al*. (*32*) have suggested that resistance to insulin-mediated glucose uptake and/or the compensatory hyperinsulinemia associated with a multimetabolic syndrome decrease urinary uric acid clearance, with a subsequent elevation of serum uric acid level. One of the limitations in our study was the lack of information on potentially important characteristics such as fasting plasma glucose and insulin level. Unfortunately, we could not determine the impact of insulin resistance on hyperuricemia in our study.

Despite the wealth of evidence that serum uric acid level is associated with a number of metabolic abnormalities, the relationship between serum uric acid level and the severity of hypertension is not yet fully understood. In our study, multivariate analysis revealed that serum creatinine level is an independent predictor of serum uric acid level in both male and female hypertensive patients. However, in all study patients, serum creatinine levels were within normal limits. Further investigations are needed to identify whether serum creatinine is merely a marker for renal dysfunction or plays a causative role in the incidence of hyperuricemia.

An elevated serum uric acid level may reflect impaired endothelial integrity, in which the endothelial-dependent vascular relaxation produced by nitric oxide is reduced. In addition, activation of the renin-angiotensin-aldosterone system in patients with essential hypertension plays important roles in the pathogenesis of myocardial hypertrophy (*33*) and the elevation of serum uric acid level. These processes contribute to the evolution of atherosclerosis (*34*, *35*). The association between LV mass and serum uric acid level, as reported in our study, provides a potential and earlier pathophysiological link to explain the increased risk of vascular events in hypertensive patients with LV hypertrophy. Both LV hypertrophy and elevated serum uric acid in hypertensive patients may be considered indicative of preclinical cardiovascular disease that may be reversed by the effective therapeutic interventions (*36*–*38*). Verdecchia *et al*. reported that the decrease in LV mass brought about by antihypertensive therapy is associated with a reduced risk for subsequent events (*36*). Furthermore, the decreasing of uric acid by allopurinol in patients with diabetes mellitus and congestive heart failure has been shown to result in improved endothelial-dependent vasodilatation (*37*). Thus, the finding that hyperuricemia and LV hypertrophy may be reversed by a pharmacological treatment may suggest a new target for therapeutic intervention in essential hypertension.

Finally, a previous prospective study has demonstrated that patients with concentric hypertrophy have a higher incidence of cardiovascular events than patients with other types of LV geometry (*10*). In the present study, the finding that the highest levels of serum uric acid were observed in our male hypertensive patients with concentric hypertrophy confirms the previous reports that these patients have the highest risk for cardiovascular morbidity and mortality (*9*–*12*).

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