Original Article

Status of Uric Acid Management in Hypertensive Subjects

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Hyperuricemia in hypertensive subjects has been considered one of risk factors of cardiovascular diseases. We investigated the status of uric acid management in 799 hypertensive subjects (432 females and 367 males; mean age 70.9 years) managed by 43 doctors (19 cardiologists and 24 noncardiologists; 25 private practice doctors and 18 hospital doctors). The serum uric acid level was available in 85.7% of the patients. This availability was equivalent regardless of facility size, and more cardiologists than noncardiologists monitored this information. The prevalence of hyperuricemia was 17.5% and was higher in men and in patients with high triglyceridemia, left ventricular hypertrophy, renal dysfunction, proteinuria, and smokers, but was not higher in subjects with chronic heart failure, diabetes mellitus, and those with prescriptions for diuretics and β-blockers. The average serum uric acid level was higher in men and patients with chronic heart failure, renal dysfunction, high triglyceridemia, low high-density cholesterolemia, smokers, and subjects prescribed β-blockers. Fifty percent of hyperuricemic patients were medicated, and 48.6% of them cleared the uric acid target level (6 mg/dL). No differences were observed in the treatment rate or the achievement rate of the target between genders, concurrent diseases, and physician specialties. Although doctors, especially cardiologists, have a high concern for the serum uric acid level, they do not intervene intensively, and specific treatment for individual patterns is not routinely given. Thus, more attention to uric acid management is necessary in hypertensive subjects to prevent cardiovascular diseases. (*Hypertens Res* 2007; 30: 549–554)

***Key Words*: hyperuricemia, hypertension, uric acid, cross-sectional investigation**

Introduction

Average serum uric acid levels and hyperuricemia prevalence are higher in hypertensive subjects than in normotensive subjects (*1*, *2*). Whether or not hyperuricemia is an independent risk factor for cardiovascular diseases (CVDs) has been debated; however, it is widely recognized as a good indicator of the incidence of CVDs (*3–6*). Especially in hypertensive subjects, several epidemiological studies have suggested that hyperuricemia may be an independent risk factor for CVDs (*6*, *7–9*). Hyperuricemia *per se* has been reported to increase blood pressure (*10–12*) and to stimulate vascular smooth muscle proliferation and vascular remodeling (*13*, *14*). Thus, the management of hyperuricemia in hypertensive subjects has been considered an important candidate to decrease the

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incidence. In Japan, guidelines for the management of hyperuricemia and gout were announced by the Japanese Society of Gout and Nucleic Acid Metabolism in 2002, and careful management of the serum uric acid level was proposed (*15*). There are few data on how doctors in Japan manage hyperuricemia in hypertensive subjects. We assessed the present status of uric acid management in hypertensive subjects and whether or not better management is necessary. In this study, we surveyed the serum uric acid level, the prevalence of hyperuricemia, and the treatment of hyperuricemia in hypertensive subjects, and we investigated the characteristics of subjects who should have their serum uric acid levels closely managed.

Methods

Study Design

A cross-sectional survey was performed for 6 months (from April to September 2005). The study protocol was approved by the Ethics Committee of Tottori University Hospital, and all of the participants followed this protocol. Forty-three doctors in 38 facilities participated in this survey (19 cardiologists: 11 at hospitals and 6 in private practice; and 24 noncardiologists: 5 at hospitals and 19 in private practice). In 2000, we investigated the serum uric acid management of 907 hypertensive subjects by cardiologists (*16*) and found that the examination rate of serum uric acid level varied substantially depending on the size of the facility (unpublished data). Therefore we compared differences in facility size and physician specialty in this investigation. A total of 799 hypertensive subjects were enrolled in this study. Hypertensive patients treated for at least 6 months prior to this survey were included. Patients treated without antihypertensive drugs were also enrolled. Excluded were patients who had been diagnosed with white coat hypertension or who had current prescriptions for antihypertensive drug(s) not for lowering blood pressure. Each participating doctor was asked to enroll consecutive outpatients who had given informed consent to participate in this study. The participating doctors were asked to complete a survey detailing how each hypertensive patient was treated. Questions for which data were unavailable were left blank; thus, a blank response indicates "no examination" or "no concurrent disease."

Study Details and Definitions

Data on age, gender, blood pressure, family history, risk factors, prescription(s), and concurrent diseases (including CVDs, cerebrovascular diseases, and renal insufficiency) were collected. Prescription details (dose, duration) were not asked except for the name of the prescription drug. Blood pressure was the mean of the blood pressure measured on the three most recent visits. Hypertension was defined as a systolic blood pressure (SBP)≥140 mmHg and/or diastolic blood pressure (DBP)≥90 mmHg. The collected laboratory data included total cholesterol, low-density lipoprotein (LDL) cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, uric acid, fasting blood sugar, glycohemoglobin and creatinine in serum, and proteinuria. Left ventricular hypertrophy (LVH) was diagnosed by ultrasound examination when end-diastolic left ventricular wall thickness was 12 mm or more, and/or by electrocardiography according to the criteria of Sokolow and Lyon index. Only patients currently smoking were defined as smokers. Renal insufficiency was defined as serum creatinine ≥1.5 mg/dL. Positive proteinuria was defined as spot proteinuria ≥100 mg/dL. Diabetes mellitus (DM) was diagnosed according to the definitions of the Japan Diabetes Society (2004). Hypercholesterolemia was defined as total cholesterol ≥220 mg/dL, LDL cholesterol ≥140 mg/dL, and/or drug treatment. Hypertriglyceridemia was defined as triglyceride ≥150 mg/dL and/or drug treatment. Low HDL cholesterolemia was defined as HDL cholesterol <40 mg/dL. Hyperuricemia was defined as a serum uric acid ≥7.0 mg/dL or treatment with uric acid–lowering drugs. Obesity was defined as a body mass index ≥25 kg/m^2.

Table 1. Patient Characteristics

A: Doctor/Facility	Subjects	Age (years)
Total	685	70.9±10.3
Hospital	298	70.1±11.0
Cardiologist	243	69.4±11.3
Non-cardiologist	55	73.2±8.8
Private clinic	387	71.0±9.7
Cardiologist	126	72.9±8.3
Non-cardiologist	261	70.1±10.2

B: Risk factors	Female (n=370)	Male (n=315)
Age (years)	72.1±10.1	68.9±10.2
Body mass index (kg/m^2)	23.9±3.6	23.7±3.1
Uric acid (mg/dL)	4.8±1.2	5.9±1.3
LDL cholesterol (mg/dL)	117.4±24.2	109.7±28.3
HDL cholesterol (mg/dL)	61.0±15.7	55.9±17.3
Triglyceride (mg/dL)	115.4±54.1	128.4±78.9
Fasted blood sugar (mg/dL)	103.3±25.3	106.5±22.1
Smoking (%)	2.4	19.4

LDL, low-density lipoprotein; HDL, high-density lipoprotein.

C: Concurrent diseases or medicine	Female (%)	Male (%)
Chronic heart failure	2.7	4.8
Ischemic heart disease	8.1	15.6
Left ventricular hypertrophy	5.1	8.9
Proteinuria	1.1	4.1
Renal dysfunction	1.6	6.7

Table 2. Prevalence of Hyperuricemia (General)

	Subjects	Prevalence (%)
Total	140	17.5
Gender		
Female	23	5.3
Male	117	31.9*
Doctor/Facility		
Hospital	78	22.7**
Cardiologist	67	24.4
Non-cardiologist	11	15.9
Private clinic	62	13.6
Cardiologist	14	10.6
Non-cardiologist	48	14.9

*$p<0.01$ *vs*. female; **$p<0.01$ *vs*. private clinic.

Statistical Analyses

Statistical analyses were performed with StatView software version 4.5 for Windows (Abacus Concepts, Berkeley, USA). Comparisons among the groups were performed with analysis of variance (ANOVA) or the χ^2 test. All values are expressed as means±SD. Values of $p<0.05$ were considered to indicate statistical significance.

Results

Examination Rate of Serum Uric Acid Level

The characteristics of the subjects are summarized in Table 1. Among the 799 subjects, the serum uric acid concentration was available in 685 subjects (85.7%, 370 women and 315 men). Among the 685 hypertensive subjects, 675 subjects (98.5%) were currently being treated with antihypertensive drug(s). The prescription rates of antihypertensive drugs were: calcium channel blockers, 76.2%; angiotensin II receptor blockers, 44.1%; angiotensin converting enzyme inhibitors, 17.8%; β-blockers (including α/β-blockers), 9.9%; α-blockers, 7.4%; diuretics, 8.2%. No differences were detected in the availability of serum uric acid examination between facilities of different sizes or between private practice and hospitals (85.1% and 86.6%, respectively). Serum uric acid was examined in 90.4% of the patients treated by a cardiologist. This rate is significantly higher that that for patients treated by noncardiologists (80.8%, $p<0.01$).

Hyperuricemia Prevalence

Among the 799 hypertensive subjects, 140 (17.5%) had complicated hyperuricemia (Table 2). Prevalence differences between gender were evident, and there was a significantly higher prevalence in men than women. We did not ask the doctors whether or not their female subjects had entered menopause, so we compared the generational differences between women over or under 55 years old and between men over or under 45 years old. Although there was no difference between men over or under 45 (data not shown), in women under 55 there were no hyperuricemic subjects. In subjects

Table 3. Prevalence of Hyperuricemia

	Prevalence (%)	*p* value
A: Risk factors		
High cholesterolemia		
(+)	15.1	n.s.
(−)	19.9	
High triglyceridemia		
(+)	35.7	0.01
(−)	19.1	
Low HDL-cholesterolemia		
(+)	24.1	n.s.
(−)	17.3	
Diabetes mellitus		
(+)	17.7	n.s.
(−)	17.5	
Obesity		
(+)	19.1	n.s.
(−)	16.7	
Family history		
(+)	13.6	n.s.
(−)	18.0	
Smoking		
(+)	26.7	0.05
(−)	16.6	
B: Concurrent disease or medicine		
Chronic heart failure		
(+)	24.2	n.s.
(−)	17.2	
Ischemic heart disease		
(+)	23.5	n.s.
(−)	16.6	
Left ventricular hypertrophy		
(+)	29.6	0.05
(−)	16.6	
Proteinuria		
(+)	41.1	0.05
(−)	17.0	
Renal dysfunction		
(+)	56.3	0.01
(−)	16.7	
Prescription of diuretics		
(+)	16.2	n.s.
(−)	17.6	
Prescription of β-blockers		
(+)	26.0	n.s.
(−)	17.0	

HDL, high-density lipoprotein.

with hypertriglyceridemia, the prevalence of hyperuricemia was significantly higher than in subjects without hypertriglyceridemia (Table 3A). There were no prevalence differences between subjects with or without high total cholesterolemia, low HDL-cholesterolemia, DM, obesity, or familial history of ischemic heart diseases (IHD) (Table 3A). No differences were detected between subjects with or without concurrent chronic heart failure (CHF) or IHD, or in those with or without diuretic or β-blocker prescriptions. However, a significant difference was observed between subjects with or without LVH, proteinuria, or renal dysfunction (Table 3B).

Depending on the facility size, the hyperuricemia prevalence was quite different. The prevalence in subjects treated in hospitals was significantly higher than those treated in private practice (22.7% and 13.6%, respectively, $p<0.01$).

Hyperuricemia Treatments

Among the 140 hyperuricemic subjects, 50.0% had been treated with medication. Of these 70 medicated subjects, 62.9% and 27.1% were prescribed a xanthine oxidase inhibitor and a uricosuric agent as monotherapy, respectively. Also, 10% of medicated subjects were treated with the combination therapy. Among the 70 treated subjects, there were no differences in the medicated rate according to gender, facility size, physician specialty, risk factors (high-LDL cholesterolemia, low-HDL cholesterolemia, DM, obesity, family history, and smoking), concurrent diseases (CHF, LVH, proteinuria, and renal dysfunction) or prescriptions (diuretics or β-blockers) (data not shown). However, the subjects of hypertriglyceridemia (66.1% *vs*. 44.1%, $p<0.01$) and IHD (75.0% *vs*. 44.8%, $p<0.05$) were more frequently treated than those without high hypertriglyceridemia or IHD.

According to the guidelines for management of hyperuricemia and gout (*15*), the target serum uric acid concentration is less than 6.0 mg/dL in both genders. We regarded the target serum uric acid concentration as 6.0 mg/dL in the following analysis. In 140 hyperuricemic subjects, 26.4% were managed under the target level. In the 70 treated subjects, 48.6% achieved the target level. There was no difference in achievement rates according to gender, facility size, or physician specialty (data not shown). On the other hand, the guidelines recommended that patients with serum uric acid concentrations greater than 8 mg/dL should be actively monitored. Among 140 hyperuricemia subjects, 9.4% of the subjects had serum uric acid levels >8.0 mg/dL (8.7% of women and 9.6% of men). This population was only 1.6% of all hypertensive subjects.

Uric Acid Level

In comparisons according to gender, the average serum uric acid concentration was significantly higher in men than women (5.9±1.3 mg/dL and 4.8±1.2 mg/dL, respectively, $p<0.01$); however, in that from subjects receiving medication, no difference was observed (6.8±1.2 mg/dL and 6.7±1.3 mg/dL, respectively).

In subjects with hypertriglyceridemia, low-HDL cholesterolemia, or a smoking habit, the average serum uric acid concentration was significantly higher than in subjects without these risk factors (5.7±1.3 mg/dL *vs*. 5.2±1.4 mg/dL, 5.7±1.2 mg/dL *vs*. 5.3±1.4 mg/dL, and 5.8±1.8 mg/dL *vs*. 5.3±1.4 mg/dL, respectively, $p<0.05$).

In subjects with CHF, renal dysfunction, or prescribed β-blockers, the average serum uric acid concentration was significantly higher than in subjects who did not have concurrent diseases or drug prescriptions (5.9±1.0 mg/dL *vs*. 5.3±1.4 mg/dL, 6.1±2.1 mg/dL *vs*. 5.3±1.3 mg/dL, and 5.9±1.4 mg/dL *vs*. 5.3±1.3 mg/dL respectively, $p<0.05$). On the other hand, the average serum uric acid concentration was similar between subjects with or without LVH or proteinuria, as well as between those with or without a prescription for diuretics.

Discussion

Examination Rate

One of the key issues in this investigation was to assess whether or not doctors actively manage patients' uric acid levels. Surprisingly, they did so for 85.7% of the 799 subjects, including 90.4% of patients treated by cardiologists. The examination rates of total cholesterol and fasting blood sugar were 95.2% and 89.1%, respectively, indicating that physicians are concerned about uric acid management. In 2000, we investigated the serum uric acid management of 907 hypertensive subjects by cardiologists (*16*). In that study, the uric acid examination rates were 57.4% in private practice and 93.2% in hospitals (unpublished data). Although we do not have data on noncardiologists in private practice in 2000, the observed difference indicated widespread concern during these 4 years from 2000 to 2004. We speculated that one reason for this difference was the introduction of proposed guidelines for the management of hyperuricemia and gout by the Japanese Society of Gout and Nucleic Acid Metabolism in 2002 (*15*). The guidelines may have enlightened and motivated doctors to manage uric acid levels.

Gender

Hyperuricemia is more prevalent in men than women, and the percentage of men with this disease (31.9%) is nearly as large as that with hyper LDL-cholesterolemia (36.5%). On the other hand, there was only a 5.3% rate of hyperuricemia in women. Although this is a small population, hyperuricemic women should be carefully managed because several epidemiological studies indicated that their lower serum uric acid levels (6.2 mg/dL) than those of men (7.5 mg/dL) are considered a threshold of cardiovascular risk for women (*5*, *7*, *8*). Also, there were no hyperuricemic subjects among women under 55 years old, indicating that much more attention

should be paid to women after menopause. As with the average serum uric acid level, the treatment rate and achievement rate of hyperuricemic subjects were similar by gender; no special attention seemed to be paid to women.

Risk Factors

Hyperuricemia was more prevalent in subjects with hypertriglyceridemia but not in those with DM, obesity, or low HDL-cholesterolemia. All four of these factors are deeply related with insulin resistance, which increases blood pressure as well as levels of triglyceride, uric acid, and blood sugar. Therefore, insulin resistance is considered the fundamental cause of hypertension. As average serum uric acid levels are high in hypertriglyceridemia and in low HDL-cholesterolemia, hyperuricemia may be observed in a relatively early stage of this syndrome.

Antihypertensive Agents

In our investigation, no differences in prevalence and average serum uric acid level were observed between subjects with and without prescribed diuretics. It is well known that diuretic therapy influences serum uric acid levels (*8*). As we did not ask for information about the dose, the reason for treatment with diuretics, or the serum uric acid concentration before treatment, we cannot explain this result. This was one limitation of our investigation. However, the influence of diuretics on hypertension management has become important. Results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) have shown that thiazide diuretics help suppress CVDs, similar to the action of calcium channel blockers and angiotensin-converting enzyme inhibitors (*17*). Also in our investigation, the prescription rate of thiazide diuretics increased from 3.9% in 2000 to 7.0% in 2004 (unpublished data), and we guess this tendency will be observed in other populations in Japan (*18*). β-Blockers are also well known to influence serum uric acid levels (*19*). In our investigation, the average serum uric acid level was significantly higher than in other studies, and the prevalence was relatively high. Thus, attention in prescribing these medications to hypertensive patients is necessary for the well being of the patient.

Concurrent Heart and Renal Diseases

Iwashima *et al*. reported that the concurrence of hyperuricemia and LVH in hypertensive patients is an independent predictor of CVD events (*20*). As this combination was also observed in our data in average serum uric acid levels and prevalence rates, we recommend that physicians assess LVH in hyperuricemic subjects by echocardiography.

As expected, serum uric acid level was significantly higher in subjects with CHF. Anker *et al*. have reported that serum uric acid level predicts the prognosis of patients with CHF (*21*). It has not been clarified whether lowering serum uric acid improves the prognosis of patients with CHF; however, xanthine oxidase inhibitors have improved the cardiac and vascular function of patients with CHF (*22*, *23*), and xanthine oxidase inhibitors are expected to improve prognosis. In this investigation, no difference was observed in the prescription rate of xanthine oxidase inhibitors between groups. There was also no difference in the rate of serum uric acid treatment between groups.

The prevalence and average serum uric acid level were high in subjects with renal dysfunction. Also, in subjects with proteinuria the average serum uric acid level was high. These results indicated that doctors did not closely manage serum uric acid levels in subjects with concurrent diseases.

Treatment

Results of the examination rate of serum uric acid levels show a high concern for uric acid management; however, the achievement rate that cleared the target uric acid level was low: 26.4%. In a separate analysis of this study for cholesterol management using the Japan Atherosclerotic Society Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Disease in 2002 (*24*), 65.0% of the hyperlipidemic patients were managed by at least one medicine, and the achievement rate was 70.6% (data not shown). These results may indicate that doctors are interested in uric acid levels but do not intend to clear the target serum uric acid level or are unaware of the specific target level. There is no strong evidence that proves the benefits of lowering serum uric acid levels to decrease CVD incidence. In absence of this evidence, doctors may be hesitant to perform intensive uric acid management.

Hypertensive subjects overproduce purine metabolites because of decreased peripheral blood perfusion (*25*); however, the main mechanism of hyperuricemia in hypertensive subjects is undersecretion of uric acid. Thus, prescription of uricosuric agents is recommended. The therapeutic strategy should be determined after identification of the mechanism of hyperuricemia in an individual pattern; however, doctors did not seem interested in this examination. Although we did not ask doctors whether or not they usually identify the individual pattern, it is extremely important to promote this examination for the careful management of hyperuricemia.

In conclusion, concern for hyperuricemia in hypertensive subjects among several different specialty physicians was confirmed. However, in general, specific treatment for individual patterns is not routinely encountered, and the treatments seemed unsatisfactory. In the Worksite Study, the effect of 1 mg/dL uric acid change on the incidence of CVDs was equivalent to a 20 mg/dL change in total cholesterol. Further, uric acid's effect on the risk of CVDs was larger than that of either cholesterol or systolic blood pressure (*5*). Careful management appropriate for individual patient situations is important in order to decrease CVDs (*26*).

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