Original Article

Hyperuricemia as a Predictor of Hypertension in a Screened Cohort in Okinawa, Japan

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Several epidemiological studies have shown a positive association between serum uric acid levels and the risk of hypertension. However, subjects in these studies were mostly men, or were incompletely examined for lifestyle-related variables. We prospectively examined the relation between hyperuricemia and the risk of developing hypertension with consideration for alcohol consumption and smoking habits in a large screened cohort of men and women. A total of 4,489 individuals (2,927 men and 1,562 women) who did not have hypertension and were not currently using antihypertensive medication were examined at the Okinawa General Health Maintenance Association in 1977. Subjects were re-examined in 2000. Hyperuricemia was defined as a serum uric acid level ≥ 7.0 mg/dl in men and ≥ 6.0 mg/dl in women. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg, and/or diastolic blood pressure (DBP) ≥ 90 mmHg. A total of 289 subjects (201 men and 88 women) were hypertensive (SBP ≥ 140 mmHg, and/or DBP ≥ 90 mmHg) in 2000. Multivariate analysis was performed for development of hypertension in hyperuricemic subjects, adjusted for age, family history of hypertension, alcohol consumption, cigarette smoking, obesity, hypercholesterolemia, hypertriglyceridemia, low high-density lipoprotein cholesterol, and diabetes mellitus. The adjusted odds ratio (95% confidence interval) in men was 1.48 (1.08–2.02) and in women was 1.90 (1.03–3.51) ($p < 0.05$, respectively). The results showed hyperuricemia to be a new predictor of hypertension development in both men and women. (*Hypertens Res* 2004; 27: 835–841)

Key Words: hyperuricemia, hypertension, metabolic syndrome, insulin resistance

Introduction

Hyperuricemia is commonly associated with hypertension (1–4). Cannon *et al.* (1) reported that hyperuricemia was present in 25% of untreated hypertensive subjects, 50% of subjects taking diuretics, and more than 75% of subjects with malignant hypertension. Schmidt *et al.* (4) showed that hyperuricemia was found more frequently in hypertensive subjects (20.1%) than in non-hypertensive subjects (6.7%), and hypertension was found more frequently in hyperuricemic subjects (60.7%) than in non-hyperuricemic subjects (30.5%).

Further, several previous studies have shown positive as-

sociations between the serum uric acid levels and the risk of development of hypertension (5–10). Selby *et al.* (5) indicated that serum uric acid was closely linked to the development of hypertension and that it might be a marker of susceptibility or an intermediate step in the pathway leading to hypertension. In the Olivetti heart study (6), serum uric acid levels were positively associated with increased risk of hypertension, but analyses were adjusted only for age, body mass index (BMI), serum total cholesterol, and serum triglyceride. Control for confounders such as lifestyle factors was incomplete.

In Japan, Nakanishi *et al.* (7) reported that the risk for development of hypertension over a 6-year period increased progressively as serum uric acid levels increased, even after

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adjustment for potentially confounding factors. Unfortunately, this study examined only male workers. Taniguchi *et al.* (9) showed that there was a positive association between serum uric acid levels and increased risk of hypertension. However, they also examined only male workers, and they lacked data for cholesterol, triglyceride, and high-density lipoprotein (HDL) cholesterol, which were considered as risk factors for atherosclerosis (11–14) and were potentially associated with insulin resistance. Insulin resistance is considered as an intermediate factor between hyperuricemia and hypertension (10).

In the present study, we examined prospectively the relation between hyperuricemia and the risk of hypertension development with consideration for smoking habits and alcohol consumption as well as other confounding factors in a large screened cohort of both men and women.

Methods

Subjects

The Okinawa General Health Maintenance Association (OGHMA) has provided data from community-based mass screenings of individuals in Okinawa, Japan, since 1973. Clinical and laboratory data have been filed in a computerized registry since 1983. Participants were screened in their residential areas, work places, or at the OGHMA clinic. Participants who visited the OGHMA clinic completed a questionnaire regarding family history of hypertension (within first-degree family members); lifestyle-related variables such as smoking and alcohol consumption; medical history; and current medications. The questionnaires were discussed during physical examinations, and a physician in the clinic further interviewed participants. Smoking habits were reviewed, and participants were classified into one of five categories: non-smoker (never smoked); ex-smoker; or current smoker of 1 to 10 cigarettes per day, 11 to 20 cigarettes per day, or more than 20 cigarettes per day. Regarding alcohol consumption, participants were classified as non-drinkers (never drank); ex-drinkers; or current drinkers of less than 1.5 cups, 1.5 to 3.0 cups, or more than 3.0 cups of alcohol per day. One cup of sake contains 15% alcohol in 180 ml. The alcohol contents of other alcoholic beverages such as whisky, wine, and beer were also calculated and 27 ml of alcohol was considered as one cup.

The 1997 and 2000 OGHMA registry data were collected from April 1, 1997, to March 31, 1998, and from April 1, 2000, to March 31, 2001, respectively. The data set included the questionnaire data and results of the screening examinations. A total of 9,914 subjects in 1997, and 11,406 subjects in 2000 participated in the “dry dock” program, a 1-day clinic run by the OGHMA. Fifty nine hundred and twenty three subjects were participants in both 1997 and in 2000. Among these 5,923 subjects, 1,434 subjects who had hypertension and who were currently using antihypertensive medication in

1997 were excluded. The 4,489 subjects (2,927 men and 1,562 women) were study subjects.

All subjects fasted overnight before blood sampling. Height and weight, blood pressure (BP), serum uric acid, serum triglyceride, serum total cholesterol, serum HDL cholesterol, fasting blood glucose (FBG), and hemoglobin A1c (HbA1c) were measured in all subjects. BMI was calculated as body weight (kg) divided by height squared (m^2). Obesity was defined as $\text{BMI} \geq 25.0 \text{ kg/m}^2$. Hyperuricemia was defined as serum uric acid $\geq 7.0 \text{ mg/dl}$ in men and $\geq 6.0 \text{ mg/dl}$ in women (15, 16). Hypertension was defined as systolic blood pressure (SBP) $\geq 140 \text{ mmHg}$, and/or diastolic blood pressure (DBP) $\geq 90 \text{ mmHg}$. Hypertriglyceridemia was defined as triglyceride level $\geq 150 \text{ mg/dl}$ (1.7 mmol/l) (17). Hypercholesterolemia was defined as a total cholesterol level of $\geq 220 \text{ mg/dl}$ (5.69 mmol/l), and low HDL cholesterol as HDL cholesterol of $< 40 \text{ mg/dl}$ in men and $< 50 \text{ mg/dl}$ in women (17). Diabetes mellitus was diagnosed if the FBG level was $\geq 126 \text{ mg/dl}$ (7 mmol/l), and/or HbA1c was $\geq 7.0\%$, or the individual was being treated for diabetes mellitus (18). The OGHMA ethics committee approved the protocol for this study. Data considered highly sensitive or personal were excluded from the original registry to protect the privacy of the screenees.

Statistical Methods

Odds ratios for hypertension development were calculated by means of univariate and multivariate logistic regression models (StatView 5.0; SAS Institute, Cary, USA). A Mann-Whitney test was used to detect statistically significant results of characteristic variables. A χ^2 test was used for statistical comparisons of the prevalence of normotensives and hypertensives in subjects with or without hyperuricemia. Univariate and multivariate logistic regression analyses were performed to assess the correlation between the risk of development of hypertension and age, obesity, hypercholesterolemia, hypertriglyceridemia, low HDL cholesterol, diabetes, hyperuricemia, family history of hypertension, smoking habit, and drinking habit. A Wilcoxon signed-ranks test was used for statistical comparisons between BP in subjects with hyperuricemia and that in subjects without hyperuricemia. A Friedman test was used for statistical comparisons between BP changes in subjects with hyperuricemia and those in subjects without hyperuricemia. Values of $p < 0.05$ were considered statistically significant.

Results

Baseline Characteristics of Study Subjects

The mean age of study subjects was 46.9 years (men, 47.6 years; women, 50.5 years; range, 18 to 89 years). The mean ($\pm$ SD) levels of serum uric acid were $6.4 (\pm 1.3) \text{ mg/dl}$ for men and $4.6 (\pm 1.1) \text{ mg/dl}$ for women. In men, serum uric acid levels were significantly higher than those of women

Table 1. Characteristics of Screened Subjects in 1997

	Elevation of BP to HT level in 2000			
	Men		Women	
	No (n = 2,726)	Yes (n = 201)	No (n = 1,474)	Yes (n = 88)
Age (years)	45.6 ± 9.1	48.6 ± 8.8*	48.8 ± 8.9	53.0 ± 8.0*
BMI (kg/m ²)	24.2 ± 2.8	25.1 ± 2.8*	23.0 ± 3.0	24.3 ± 2.9*
SBP (mmHg)	115.7 ± 10.1	125.1 ± 8.3*	112.0 ± 11.8	126.4 ± 8.5*
DBP (mmHg)	72.4 ± 7.8	78.9 ± 6.5*	68.5 ± 8.0	77.5 ± 6.6*
PP (mmHg)	43.3 ± 7.6	46.2 ± 7.5*	43.5 ± 7.9	48.8 ± 7.7*
Cr (mg/dl)	1.1 ± 0.1	1.1 ± 0.1	0.8 ± 0.1	0.9 ± 0.1
UA (mg/dl)	6.4 ± 1.3	6.6 ± 1.5*	4.6 ± 1.0	6.1 ± 1.1*
TC (mg/dl)	203.6 ± 33.9	209.4 ± 38.2*	207.9 ± 36.8	210.2 ± 33.5
TG (mg/dl)	160.8 ± 122.0	176.4 ± 186.1	100.6 ± 63.8	104.0 ± 66.0
HDL (mg/dl)	52.3 ± 13.0	52.7 ± 13.6	62.8 ± 14.4	60.7 ± 13.6
FBG (mg/dl)	102.5 ± 17.9	105.3 ± 19.5*	96.8 ± 12.9	98.7 ± 13.1
Family history of HT (%)	17.8	25.9*	25.3	38.6*
Current smokers (%)	45.8	32.3*	5.0	5.7
Current drinkers (%)	87.6	89.6	29.0	21.6

BP, blood pressure; HT, hypertension; BMI, body mass index; SBP, systolic BP; DBP, diastolic BP; PP, pulse pressure; UA, uric acid; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; FBG, fasting blood glucose. Data are the mean ± SD. * $p < 0.05$.

($p < 0.001$). A total of 1,095 (24.4%) individuals (955 men, 140 women) were diagnosed with hyperuricemia. The mean age of hyperuricemic men was 46.5 years and of hyperuricemic women was 53.7 years.

The baseline characteristics of subjects in 1997 are summarized by gender according to the BP status in 2000 in Table 1. Of the 4,489 subjects, 289 (201 men, 88 women) developed hypertension during the 3 years of the study. The incidence of BP elevation from normotension to hypertension was 6.3% (6.9% in men; 5.6% in women). Among men, normotensives who developed hypertension in 2000 (male hypertension group) were significantly older than normotensives who remained normotensive (male normotension group). Baseline BMI, SBP, DBP, uric acid level, total cholesterol level, and FBG level were also higher in the former group than in the latter. The male hypertension group also had significantly higher prevalence of family history of hypertension and lower prevalence of current smokers. Among women, normotensives who developed hypertension (female hypertension group) were significantly older than normotensives who remained normotensive (female normotension group). In the female hypertension group, baseline BMI, SBP, DBP, and uric acid level were higher, and there was a higher prevalence of family history of hypertension compared with the female normotension group.

Effect of Hyperuricemia on the Development of Hypertension

While 119 (6.0%) of the men without hyperuricemia in 1997 ($n = 1,972$) developed hypertension, 82 (8.6%) of the sub-

jects with hyperuricemia ($n = 955$) developed hypertension. Among women without hyperuricemia in 1997 ($n = 1,422$), 72 (5.1%) developed hypertension. Among women with hyperuricemia ($n = 140$), 16 (11.4%) developed hypertension. Hypertension was found significantly more often in subjects with hyperuricemia than in subjects without hyperuricemia in both men ($p = 0.0018$) and women ($p = 0.0105$).

Univariate and Multivariate Analysis

Results of univariate and multivariate logistic regression analyses for development of hypertension in the presence of hyperuricemia and other variables are shown for men in Table 2 and for women in Table 3. Age, obesity, hyperuricemia, and a family history of hypertension were significantly associated with the development of hypertension in both men and women. Habitual smoking had a significantly negative correlation with the development of hypertension only in men. In multivariate analysis, hypercholesterolemia, hypertriglyceridemia, low HDL cholesterol, diabetes, and alcohol consumption had no significant association with the development of hypertension.

BP Levels in Subjects with or without Hyperuricemia

Figure 1 shows BP levels for men and women with or without hyperuricemia. Small but statistically significant increases in SBP and decreases in DBP from 1997 to 2000 were observed in subjects without hyperuricemia in both sexes. Men with hyperuricemia showed no significant change in SBP and DBP. However, women with hyperuricemia had a sig-

Table 2. Risk of Development of Hypertension in Men According to Presence of Hyperuricemia and Other Variables by Univariate and Multivariate Analysis

Variables	Univariate		Multivariate	
	OR	95% CI	OR	95% CI
Age	1.04 (1.02–1.05)*		1.04 (1.02–1.05)*	
Obesity	1.56 (1.17–2.08)*		1.54 (1.14–2.08)*	
Hypercholesterolemia	1.38 (1.02–1.86)*		1.24 (0.90–1.69)	
Hypertriglyceridemia	0.97 (0.72–1.30)		0.92 (0.67–1.28)	
Low HDL cholesterol	1.57 (0.98–2.51)		1.62 (0.98–2.67)	
Diabetes mellitus	1.47 (0.86–2.50)		1.29 (0.74–2.24)	
Hyperuricemia	1.46 (1.09–1.96)*		1.49 (1.09–2.03)*	
Family history of HT	1.61 (1.16–2.24)*		1.66 (1.19–2.32)*	
Smoking habit	0.57 (0.42–0.77)*		0.66 (0.48–0.91)*	
Drinking habit	1.21 (0.76–1.93)		1.41 (0.87–2.27)	

OR, odds ratio; CI, confidence interval; HDL, high-density lipoprotein; HT, hypertension. * $p < 0.05$.

Table 3. Risk of Development of Hypertension in Women According to Presence of Hyperuricemia and Other Variables by Univariate and Multivariate Analysis

Variables	Univariate		Multivariate	
	OR	95% CI	OR	95% CI
Age	1.05* (1.03–1.08)		1.06* (1.03–1.09)	
Obesity	2.75* (1.78–4.27)		2.39* (1.51–3.79)	
Hypercholesterolemia	0.94 (0.60–1.48)		0.67 (0.41–1.10)	
Hypertriglyceridemia	0.88 (0.47–1.65)		0.62 (0.31–1.25)	
Low HDL cholesterol	0.88 (0.51–1.51)		0.96 (0.53–1.77)	
Diabetes mellitus	1.59 (0.48–5.29)		1.24 (0.36–4.29)	
Hyperuricemia	2.42* (1.36–4.28)		1.94* (1.05–3.57)	
Family history of HT	1.86* (1.19–2.90)		2.26* (1.42–3.60)	
Smoking habit	1.14 (0.45–2.89)		1.65 (0.62–4.38)	
Drinking habit	0.68 (0.40–1.14)		0.83 (0.47–1.47)	

OR, odds ratio; CI, confidence interval; HDL, high-density lipoprotein; HT, hypertension. * $p < 0.05$.

Fig. 1. Blood pressure levels in subjects with and without hyperuricemia. HUA, hyperuricemia, serum uric acid level ≥ 7.0 mg/dl in men and ≥ 6.0 mg/dl in women; SBP, systolic blood pressure; DBP, diastolic blood pressure. * $p < 0.05$ by multiple logistic analysis. ** Controls for age, BMI, DBP, HDL, TG, habitual smoking, habitual drinking, and family history of hypertension.

nificantly larger increase in SBP from 1997 to 2000 (increase in SBP: 2.4 mmHg) than women without hyperuricemia (increase in SBP: 0.8 mmHg). The change of SBP in subjects with hyperuricemia from 1997 to 2000 was larger in the female hypertensive group than in the male hypertensive group (20 mmHg vs. 14 mmHg).

Discussion

We revealed in this prospective cohort study that hyperuricemia was associated with incident hypertension, even after adjustment for age, obesity, hypercholesterolemia, hyper-

triglyceridemia, low HDL cholesterol, diabetes, family history of hypertension, habitual smoking, and alcohol consumption in both men and women. Several previous studies have shown positive correlations between the serum uric acid levels and the risk of hypertension (5–10). However, subjects in these studies were mainly men, or were incompletely examined for lifestyle-related variables. In the present study, metabolic disorders and lifestyle-related variables such as smoking and alcohol consumption were examined, and hyperuricemia was a strong and an independent risk factor for predicting the development of hypertension in women as well as in men. Although Selby *et al.* (5) indicated that there was a positive association between serum uric acid levels and increased risk of hypertension in both men and women, they examined the association in a case-control study.

In Japanese, hyperuricemia has been defined as serum uric acid ≥ 7.0 mg/dl in both men and women (19). However, these criteria were based on the physical character of urate, and the distribution of serum uric acid level was different in men and women in the present study. We therefore defined hyperuricemia as serum uric acid ≥ 7.0 mg/dl in men and ≥ 6.0 mg/dl in women according to previous reports (15, 16).

In the present study, the increase in SBP of the hyperuricemic women from 1997 to 2000 was significantly larger than that of the non-hyperuricemic women. The change of SBP in subjects with hyperuricemia was also larger in the female hypertensive group than in the male hypertensive group. The adjusted odds ratio for risk of development of hypertension in women was larger than that of men (1.90 vs. 1.48). Such results have not been shown in previous studies. The role of hyperuricemia in the difference in BP change between men and women was unclear. Sex hormones may influence the relation between hyperuricemia and the development of hypertension (20). In the present study, the distribution of serum uric acid level was different in men and women, and the average serum uric acid level was higher in men than in women (6.4 mg/dl vs. 4.5 mg/dl). The uric acid level used to define hyperuricemia was relatively higher in women than in men (7.0 mg/dl vs. 6.0 mg/dl). Thus hyperuricemia may have had a stronger effect on the elevation of SBP in women than in men in the present cohort.

While the present study showed that hyperuricemia in men was also a significant and independent predictor of the development of hypertension, men with hyperuricemia showed no significant increase in SBP from 1997 to 2000. We considered that this result may have been due to the small difference in the rate of development of hypertension in men between the subjects with and those without hyperuricemia in men (hyperuricemic: 8.6%; non-hyperuricemic: 6.0%) compared with the difference in the rate of development of hypertension between the subjects with and those without hyperuricemia in women (hyperuricemic: 11.4%; non-hyperuricemic: 5.1%).

The hypertension group was older than the normotension group, and the hypertension group had a higher baseline

BMI, SBP, DBP, serum uric acid level, and prevalence of family history of hypertension, as well as a significantly higher prevalence of hyperuricemia, than the normotension group in both men and women (Table 1). On the other hand, after controlling for potential risk factors, the association of hyperuricemia with the development of hypertension persisted in both men and women (Tables 2 and 3). Hyperuricemia is positively associated with obesity, hypertension, and dyslipidemia in both men and women, and subjects with hyperuricemia tend to have a clustering of these cardiovascular risk factors (21). It is likely that hyperuricemia had an influence on the baseline characteristics of the present study.

How serum uric acid increases the risks of hypertension remains to be elucidated. Several recent experimental studies showed that systemic hypertension developed in hyperuricemic rat models (22–25). Watanabe *et al.* (22) showed that mild hyperuricemia in rats increased BP acutely through a renin-dependent mechanism. They also showed that chronic hyperuricemia caused salt sensitivity, in part by inducing preglomerular vascular disease. Hypertension was prevented by administration of an angiotensin-converting enzyme inhibitor, and to a lesser extent by L-arginine (a precursor to nitric oxide), thereby confirming that the renin-angiotensin system and the nitric oxide synthesis system play key roles in BP elevation. Saito *et al.* (14) reported that serum uric acid levels in humans correlated with plasma renin activity. Hyperuricemic rats have also been shown to have salt sensitivity (22). Another experimental study showed that salt sensitivity might result from preglomerular vascular disease (26). The experimental models with associated preglomerular vascular disease had renal ischemia, altering the balance of local vasoconstriction, and resulting in reduced sodium excretion and increased BP. Hyperuricemia may contribute to endothelial dysfunction (27), free radicals (28), and oxidative stress (29, 30).

Insulin resistance is suspected to decrease the tubular secretion of urate (31). Modan *et al.* (32) reported that hyperuricemia is a feature of hyperinsulinemia/insulin resistance. Insulin stimulates tubular sodium-hydrogen exchange and exerts a direct effect on renal sodium reabsorption. These observations suggest links between hyperuricemia, hypertension, and insulin resistance. Unfortunately, we could not directly test the association between renal involvement, plasma renin activity, salt-sensitivity, endothelial dysfunction, or insulin resistance and the development of hypertension in this cohort. However, the present study showed that obesity, a main feature of insulin resistance, was a predictor of development of hypertension. Further investigations will be needed to explain the pathogenetic roles of hyperuricemia in the development of hypertension.

Family history of hypertension is associated with increased risk of hypertension (33–35). Tozawa *et al.* (35) showed in a prospective study that family history of hypertension was a significant predictor of BP elevation. In the present study, a significant association was recognized be-

tween family history of hypertension and the development of hypertension. The results suggest that genetic factors have a strong influence on the development of hypertension.

In the present study, habitual smoking correlated negatively with the development of hypertension in men. Cigarette smoking induces an acute rise in BP (36). Nicotine acts as an adrenergic agonist, mediating local and systemic catecholamine release and possibly the release of vasopressin (36). We speculated that a complex interaction between age, BMI, and alcohol intake is likely to affect the relation between smoking and BP (37).

Previous epidemiological studies revealed a linear-response relationship between alcohol consumption and BP (38, 39). On the other hand, some authors have speculated that ingestion of smaller quantities of alcohol may reduce BP (40, 41). The present study indicated no significant association between alcohol consumption and the development of hypertension. We speculate that the short duration of the follow-up period of the present study affected the association between alcohol consumption and the development of hypertension.

Several limitations of this study should be considered. Serum uric acid and BP were measured only once on the screening day. Although the serum uric acid levels nearly conformed to the standard normal distribution patterns in both men and women (data not shown), it is possible that many confounding factors that we did not measure were associated with serum uric acid in our cohort. For example, we did not evaluate dairy in the diets of the study subjects, and there are several drugs that may also have affected the results. Diuretics, such as thiazides, increase serum uric acid levels by stimulating urate reabsorption in the proximal tubules (42). Hyperuricemia is present in 50% of subjects taking diuretics (43). We have no data on diuretic use in the present study. The subjects with hypertension in 2000 may have had diuretic-induced hyperuricemia, which could have resulted in underestimation of the association between hyperuricemia and hypertension. Further, antihyperuricemic agents may have been given to subjects with hyperuricemia. We also had no data on the use of these agents in the present study, and thus may have underestimated the prevalence of hyperuricemia. Serum uric acid concentration is influenced by the rate of production on the one hand (44), and the rate of elimination on the other (45). Facchini *et al.* suggested that urinary uric acid clearance decreased in proportion to the increase in insulin resistance, leading to an increase in serum uric acid concentration (31). However, we did not measure the rate of production or the rate of elimination of uric acid. We also did not distinguish gout from asymptomatic hyperuricemia in the subjects with hyperuricemia in the present study. In women, serum uric acid has been shown to increase after menopause (46). In the present study, the mean age of hyperuricemic women was 53.0 years, which suggested that a large number of the hyperuricemic women may have been in the postmenopausal period. Unfortunately, however, we were not able to assess the influence

of menopause on serum uric acid level in women in the present study. Another limitation was that the participants of the present study were relatively healthy and were concerned with their health status. Finally, other potential confounders, such as income and social status, were not examined. These limitations may explain the differences between our results and those of other population-based studies (6–10).

In conclusion, we showed that hyperuricemia was significantly associated with the development of hypertension in both men and women in a screened cohort in Okinawa, Japan. Recognizing and addressing hyperuricemia may be necessary for the primary prevention of hypertension.

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