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Hypertension

Association of Serum Uric Acid with Cardiovascular Disease in Taiwanese Patients with Primary Hypertension

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Background: Hyperuricemia is closely linked to hypertension and may be a marker of susceptibility or an intermediate step in the development of metabolic syndrome. However, recently, there have been conflicting conclusions regarding the independent role of uric acid as a risk factor of cardiovascular disease (CVD). The specific role of serum uric acid (SUA) in relation to CVD remains controversial, and there are limited reports utilizing Asian data available on this issue. Therefore, this study investigated the association between SUA and cardiovascular disease in Taiwanese patients with essential hypertension.

Methods: There were 3472 participants from 55-80 years of age (1763 males, 1709 females) from 38 sites across Taiwan in this hospital-based cross-sectional study, covering the period November 2005 to December 2006. The CVD included diagnosed angina pectoris, myocardial infarction, congestive heart failure, and stroke.

Results: Hyperuricemia is positively associated with CVD in both sexes when a unified cut-off SUA level of 7 mg/dl was used. However, the odds ratios (ORs) for all CVD were greater in magnitude in hypertensive women than in men when there was co-morbidity of diabetes. The ORs of all CVD in the diabetes subgroup were statistically significantly ($p = 0.01$ for women, $p = 0.07$ for men). By multivariate analysis, hyperuricemia did not confer an increased risk of CVD.

Conclusions: Hyperuricemia may be associated with increased risk of CVD, but is not an independent risk factor of CVD in essential hypertensive Taiwanese patients.

Key Words: Cardiovascular disease • Hypertension • Hyperuricemia • Uric acid

INTRODUCTION

Worldwide epidemiologic studies have shown that hyperuricemia is associated with many traditional cardiovascular risk factors that characterize the so-called metabolic syndrome (MS).[1-3] Recent studies reveal that hyperuricemia is positively associated with obesity, hypertension, and dyslipidemia, and that patients tend to have a clustering of these cardiovascular risk factors.[4,5] Because of various risk factors and the close association with serum uric acid (SUA), proving or excluding an independent role of hyperuricemia using multivariable analysis has been exceedingly difficult. Although some reports disputed the relationship between hyperuricemia

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and clinical events, half of these studies showed a significant and independent association between SUA and CVD, at least in a major sub-group (i.e. women or patients with ischemic heart disease).[6-8] However, the magnitude of excess risk attributable to hyperuricemia is likely to be small in healthy individuals.

The specific role of SUA in relation to CVD remains unclear. Studies on Asian subjects, who differ physically from Caucasians, are also relatively rare. The present study was designed to determine the association of SUA with the risk of CVD after controlling for traditional and established risk factors by multivariate analyses in this large cohort of Taiwanese patients with essential hypertension.

METHODS

Participants

All study participants were enrolled from the outpatient clinics of the cardiology or neurology departments of participating study sites in this cross-sectional, single visit, multi-center study. The total study duration was 12 months, and the patient enrollment period was 6 months. A sample of 3472 hypertensive participants from 55-80 years old (1763 males, 1709 females) was obtained from 38 sites across Taiwan during the period of November 2005 to December 2006. The participants all had a hypertension diagnosis (at least two blood pressure measurements performed more than 30 min. apart were > 140/90 mmHg) or were regularly taking anti-hypertensive medications or had objective evidence of target organ damage (i.e., brain, retina, kidney, or heart) due to essential hypertension.

After providing a signed informed consent, each participant underwent a structured interview, which included: a questionnaire; blood sampling (after an overnight fast) for glucose, uric acid and lipid determinations; urine sampling for albumin and creatinine; an electrocardiogram (ECG) and a physical examination with measurement of seated blood pressure, body height, body weight, and waist circumference. Blood pressure was measured by trained physicians or nurses, with participants in a seated position after resting for at least 5 min. Patient body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was measured on standing subjects with a soft tape midway between the lowest rib and the iliac crest.

The questionnaire included inquiries about age, sex, education, cigarette smoking, exercise, a self-reported history of duration of hypertension and anti-hypertensive drug treatment, congestive heart failure (CHF), angina pectoris, myocardial infarction (MI), diabetes mellitus, and prior stroke/transient ischemic attack. Angina (coronary heart disease) and stroke were defined using the WHO MONICA criteria. MI was diagnosed by a representative set of ECG, cardiac enzyme values, and typical symptoms. Angina was defined as the use of nitroglycerine, experience of typical chest pain, and ECG changes compatible with ischemic heart disease. Stroke was defined as an event requiring hospitalization and was verified from local hospital records. Undetermined cases were confirmed using computed tomography and magnetic resonance imaging.

Statistical analysis

Baseline characteristics across categories of hyperuricemia were compared using Kruskal-Wallis tests for continuous variables and χ^2 tests for categorical variables. The primary analysis assessed the association between uric acid level and CVD. Cox proportional hazards models were constructed to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for uric acid level as a continuous measure and across categories. Patients without elevated uric acid level were chosen as the reference group for all analyses. Risk-adjusted models were further made for a broad range of potential confounders pre-specified based on previous CVD association studies (i.e., body mass index, smoking, and a history of hypercholesterolemia, hypertension, or diabetes) and randomized treatment assignment.

SUA levels were categorized into four quartiles: ≤ 5 mg/dl (reference), 5.1-7 mg/dl, 7.1-9 mg/dl, and > 9 mg/dl. Hyperuricemia was defined as SUA levels > 7.0 mg/dl, while hypercholesterolemia was defined as total cholesterol levels ≥ 200 mg/dl. Hypertriglycemia was defined as triglyceride levels ≥ 150 mg/dl. Hypertension was defined as systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or the use of anti-hypertensive drugs. Diabetes was defined as fasting blood sugar > 126 mg/dl or the use of anti-diabetic medications.

Multiplicative interaction terms between uric acid level and various baseline characteristics were evaluated in the fully adjusted models using likelihood ratio tests. Tests for any linear trend were performed by assigning all of the patients' uric acid level in a respective category. Deviation from linearity was tested by including a quadratic term in the trend model and by comparing a model containing indicator variables for all categories of uric acid level with models containing a linear term for these categories using a likelihood ratio test with 2 degrees of freedom. The model fit of a threshold-effect model (uric acid level > 7.0 mg/dl vs. ≤ 7 mg/dl) was also compared to the indicator variable model. The population-attributable risk related to excessive uric acid level was estimated using standard methods. All analyses were performed using the SAS version 9 (SAS Institute Inc, Cary, North Carolina). A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics stratified by increasing levels of uric acid were shown in Table 1. Overall, 765 patients (22.52%) had SUA ≤ 5 mg/dl (reference), 1572 (46.28%) had SUA 5.1-7 mg/dl, 838 (24.67%) had SUA 7.1-9 mg/dl, and 222 (6.54%) had SUA > 9 mg/dl. Waist circumference, BMI, and hypertriglycemia increased as SUA level elevated.

There were 310 (40.52%), 644 (40.97%), 415 (49.52%), and 114 (51.35%) all CVD events among patients with SUA level ≤ 5 mg/dl (reference), 5.1-7 mg/dl, 7.1-9 mg/dl, and > 9 mg/dl, respectively (Table 2). In terms of all CVD, the univariate-adjusted ORs were 1.44 (95% CI, 1.18-1.76), and 1.55 (95% CI, 1.15-2.09) for patients with SUA level 7.1-9 mg/dl and > 9 mg/dl, respectively. This indicated that hyperuricemia remained significantly associated with increased risk of all CVD. Analyzing the cardiovascular event by separating to angina, MI, stroke, and CHF produced concordant results except for stroke, compared to patients with SUA level ≤ 7.0 mg/dl.

After multivariate adjustment, uric acid level > 7.0 mg/dl became insignificantly associated with increased risk of all cardiovascular events. The multivariate-adjusted ORs were 0.98 (95% CI, 0.65-1.48) and 0.89 (95% CI, 0.48-1.64) for patients with SUA level 7.1-9 mg/dl and > 9 mg/dl, respectively. Testing the difference between CVD sub-groups, the ORs for angina, MI, stroke, and CHF were statistically insignificant.

The findings appeared to be consistent across all major sub-groups evaluated, although the power to detect subgroup effects was limited (Table 3, 4). Although most individual risk estimates were not statistically significant, hyperuricemia > 7 or > 9 mg/dl was consistently associated with an increased risk of cardiovascular events across different categories of hypercholesterolemia, and hypertriglycemia. Risk of CVD also increased in patients with hyperuricemia regardless of age, BMI,

Table 1. Baseline patient characteristics, by quartile of serum uric acid level

Characteristic n = 3,397	Serum uric acid levels No. (%)			
	≤ 5.0 mg/dl n = 765 (22.52%)	5.1-7.0 mg/dl n = 1,572 (46.28%)	7.1-9.0 mg/dl n = 838 (24.67%)	> 9.0 mg/dl n = 222 (6.54%)
Age, y	66.9 ± 6.7	67.1 ± 6.9	68.0 ± 7.3	68.0 ± 7.0
Body mass index*	25.3 ± 3.5	26.1 ± 3.6	26.7 ± 3.8	27.1 ± 4.4
Waist circumference,cm	89.1 ± 10.3	91.8 ± 10.2	93.8 ± 9.9	95.3 ± 9.9
Duration of hypertension				
< 1 year	76 (9.93%)	126 (8.03%)	63 (7.56%)	21 (9.46%)
1-5 year	277 (36.21%)	536 (34.16%)	245 (29.41%)	54 (24.32%)
> 5 year	412 (53.86%)	907 (57.81%)	525 (63.03%)	147 (66.22%)
Diabetes mellitus	253 (33.07%)	445 (28.31%)	252 (30.07%)	65 (29.28%)
Cholesterol, mg/dl	196.1 ± 37.7	195.0 ± 37.7	198.0 ± 41.8	200.3 ± 43.4
Triglyceride, mg/dl	138.3 ± 90.0	149.6 ± 116.1	155.4 ± 94.6	178.3 ± 112.8
Blood sugar, mg/dl	123.7 ± 47.5	118.7 ± 41.0	118.3 ± 39.9	119.9 ± 39.7

* Calculated as weight in kilograms divided by height in meters squared.

Table 2. Uric acid level and risk of cardiovascular events

Relative risk		Serum uric acid levels No.(%)			
OR (95%CI) n = 3,397		≤ 5.0 mg/dl n = 765 (22.52%)	5.1-7.0 mg/dl n = 1,572 (46.28%)	7.1-9.0 mg/dl n = 838 (24.67%)	> 9.0 mg/dl n = 222 (6.54%)
All CVD.	No. (%)	310 (40.52%)	644 (40.97%)	415 (49.52%)	114 (51.35%)
	Univariate	1 (Reference)	1.02 (0.85-1.21)	1.44 (1.18-1.76)#	1.55 (1.15-2.09)#
	Multivariate-adjusted*	1	0.96 (0.67-1.38)	0.98 (0.65-1.48)	0.89 (0.48-1.64)
Angina	No. (%)	126 (16.47%)	314 (19.97%)	186 (22.20%)	50 (22.52%)
	Univariate	1	1.25 (0.996-1.57)	1.44 (1.12-1.85)#	1.46 (1.01-2.11)#
	Multivariate-Adjusted*	1	1.33 (0.76-2.33)	1.35 (0.72-2.52)	1.32 (0.55-3.17)
MI	No. (%)	31 (4.05%)	79 (5.03%)	60 (7.16%)	20 (9.01%)
	Univariate	1	1.24 (0.81-1.90)	1.82 (1.17-2.85)#	2.34 (1.30-4.19)#
	Multivariate-adjusted*	1	0.92 (0.39-2.16)	0.85 (0.33-2.20)	1.08 (0.30-3.86)
Stroke	No. (%)	156 (20.39%)	300 (19.08%)	188 (22.43%)	52 (23.42%)
	Univariate	1	0.93 (0.75-1.15)	1.14 (0.90-1.45)	1.21 (0.84-1.73)
	Multivariate-adjusted)*	1	0.94 (0.62-1.43)	1.02 (0.64-1.62)	0.82 (0.41-1.66)
CHF	No. (%)	45 (5.88%)	100 (6.36%)	79 (9.43%)	33 (14.86%)
	Univariate	1	1.08 (0.75-1.55)	1.67 (1.14-2.45)#	2.75 (1.71-4.44)#
	Multivariate-adjusted	1	1.03 (0.47-2.25)	1.01 (0.42-2.46)	1.46 (0.45-4.68)

*Adjusted for age, BMI, waist circumference, diabetes, hypercholesterolemia, hypertriglycemia, smoking, and sex. # Statistically significant ($p < 0.05$). BMI, body mass index; CHF, congestive heart failure; MI; myocardial infarction; OR, odds ratio.

Table 3. Various risk factors and the association with all cardiovascular events

Characteristic n = 3,397	All CVD/patients (%)	Serum uric acid levels, No. (%)			
		≤ 5.0 mg/dl n = 765 (22.52%)	5.1-7.0 mg/dl n = 1,572 (46.28%)	7.1-9.0 mg/dl n = 838 (24.67%)	> 9.0 mg/dl n = 222 (6.54%)
Age > 60 y	Yes (n = 2702)	261/609 (42.86%)	527/1239 (42.53%)	346/674 (51.34%)	95/180 (52.78%)
	No (n = 695)	49/156 (31.41%)	117/333 (35.14%)	69/164 (42.07%)	19/42 (45.24%)
Body mass	Yes (n = 468)	30/73 (41.10%)	86/196 (43.65%)	88/155 (56.77%)	26/43 (60.47%)
Index* ≥ 30 kg/m^2	No (n = 2907)	275/685 (40.15%)	556/1365 (40.73%)	327/681 (48.02%)	87/176 (49.43%)
Waist circumference	Yes (n = 1672)	124/298 (41.61%)	336/759 (44.27%)	250/478 (52.30%)	68/137 (49.64%)
≥ 92 cm	No (n = 1702)	181/461 (39.26%)	303/803 (37.73%)	161/354 (45.48%)	45/84 (53.57%)
History of hypertension	Yes (n = 1991)	174/412 (42.23%)	372/907 (41.01%)	272/525 (51.81%)	74/147 (50.34%)
> 5 years	No (n = 1398)	136/353 (38.53%)	269/662 (40.63%)	140/308 (45.45%)	40/75 (53.33%)
Diabetes mellitus	Yes (n = 1015)	119/253 (47.04%)	200/445 (44.94%)	144/252 (57.14%)	36/65 (55.38%)
	No (n = 2356)	188/507 (37.08%)	438/1116 (39.25%)	266/578 (46.02%)	76/155 (49.03%)
Hypercholesterolemia	Yes (n = 2582)	236/602 (39.20%)	470/1192 (39.43%)	301/626 (48.08%)	79/162 (48.77%)
≥ 150 mg/dl	No (n = 281)	38/68 (55.88%)	63/126 (50.00%)	42/70 (60.00%)	11/17 (64.71%)
Hyper-triglycemia	Yes (n = 428)	26/72 (36.11%)	78/192 (40.63%)	64/122 (52.46%)	20/42 (47.62%)
≥ 150 mg/dl	No (n = 697)	70/156 (44.87%)	148/327 (45.26%)	72/178 (40.45%)	17/36 (47.22%)
Smoking	Yes (n = 463)	45/84 (53.57%)	99/198 (50.00%)	81/146 (55.48%)	18/35 (51.43%)
	No (n = 2926)	264/680 (38.82%)	544/1370 (39.71%)	332/689 (48.19%)	96/187 (51.34%)
Sex	Male (n = 1725)	130/263 (49.43%)	364/771 (47.21%)	287/536 (53.54%)	86/155 (55.48%)
	Female (n = 1672)	180/502 (35.86%)	280/801 (34.96%)	128/302 (42.38%)	28/67 (41.79%)

* Calculated as weight in kilograms divided by height in meters squared.

waist circumference, and presence of diabetes. None of the sub-groups revealed an increased risk of cardiovascular events if SUA level was ≤ 7.0 mg/dl. Accordingly, corresponding CIs widely overlapped and none of the p values for interaction were statistically significant, except in the sub-group of hypertriglycemia when their

Table 4. Level of uric acid and risk of cardiovascular events, stratified by baseline characteristics

Characteristic n = 3,397	OR[a] (95% CI)	Serum uric acid levels, No. (%)			
		≤ 5.0 mg/dl n = 765 (22.52%)	5.1-7.0 mg/dl n = 1,572 (46.28%)	7.1-9.0 mg/dl n = 838 (24.67%)	> 9.0 mg/dl n = 222 (6.54%)
Age > 60 y	Yes (n = 2702)	1 (Reference)	0.99 (0.81-1.20)	1.41 (1.13-1.75)*	1.49 (1.07-2.08)*
	No (n = 695)	1 (Reference)	1.18 (0.79-1.78)	1.59 (1.003-2.51)*	1.80 (0.90-3.62)
Body mass index	Yes (n = 468)	1 (Reference)	1.11 (0.64-1.92)	1.88 (1.07-3.31)*	2.19 (1.02-4.73)*
≥ 30 kg/m^2	No (n = 2907)	1 (Reference)	1.03 (0.85-1.24)	1.38 (1.11-1.71)*	1.46 (1.05-2.03)*
Waist circumference	Yes (n = 1672)	1 (Reference)	1.12 (0.85-1.46)	1.54 (1.15-2.06)*	1.38 (0.92-2.08)
≥ 92 cm	No (n = 1702)	1 (Reference)	0.94 (0.74-1.19)	1.29 (0.98-1.71)	1.79 (1.12-2.85)*
History of hypertension	Yes (n = 1991)	1 (Reference)	0.95 (0.75-1.20)	1.47 (1.13-1.91)*	1.39 (0.95-2.02)
> 5 years	No (n = 1398)	1 (Reference)	1.09 (0.84-1.42)	1.33 (0.98-1.81)	1.82 (1.10-3.01)*
Diabetes mellitus	Yes (n = 1015)	1 (Reference)	0.92 (0.67-1.25)	1.50 (1.06-2.13)*	1.40 (0.81-2.42)
	No (n = 2356)	1 (Reference)	1.10 (0.88-1.36)	1.45 (1.13-1.85)*	1.63 (1.14-2.35)*
Hypercholesterolemia	Yes (n = 2582)	1 (Reference)	1.01 (0.83-1.23)	1.44 (1.15-1.80)*	1.48 (1.04-2.09)*
≥ 150 mg/dl	No (n = 281)	1 (Reference)	0.79 (0.44-1.43)	1.18 (0.60-2.33)	1.45 (0.48-4.37)
Hypertriglycemia	Yes (n = 428)	1 (Reference)	1.21 (0.69-2.12)	1.95 (1.07-3.55)*	1.61 (0.74-3.49)
≥ 150 mg/dl	No (n = 697)	1 (Reference)	1.02 (0.69-1.49)	0.84 (0.54-1.29)	1.10 (0.53-2.27)
Smoking	Yes (n = 463)	1 (Reference)	0.87 (0.52-1.45)	1.08(0.63-1.85)	0.92 (0.42-2.02)
	No (n = 2926)	1 (Reference)	1.04 (0.86-1.25)	1.47 (1.18-1.82)*	1.66 (1.20-2.30)*
Sex	Male (n = 1725)	1 (Reference)	0.92 (0.69-1.21)	1.18 (0.88-1.58)	1.28 (0.86-1.90)
	Female (n = 1672)	1 (Reference)	0.96 (0.76-1.21)	1.32 (0.98-1.76)	1.28 (0.77-2.16)

[a] ORs are adjusted for age, sex, BMI, waist circumference, diabetes, hypercholesterolemia, hyper-triglycemia, and smoking.
BMI, body mass index; OR, odds ratio.

SUA level was 7.1-9.0 mg/dl (p = 0.02, data not shown).

Sex effect

The ORs for hyperuricemia and CVD in both gender compared to the reference group (first quartile ≤ 5 mg/dl) were statistically significant in the third and fourth SUA level quartiles (p ≤ 0.001 for quartile 3, p = 0.004 for quartile 4), but not in the sub-groups of males and females (Table 5). The correlation observed between SUA and CVD in females did not confirm previous studies.[9] The ORs of hyperuricemia for all CVD were the same in magnitude in females and in males when the four quartiles of SUA level were used were all statistically insignificant in both sexes. This upward curve was less apparent in both sexes and a clear dose-response trend was not seen. Nonetheless, this finding warranted some caution in terms of interpretation because of the small number of patients in some subgroups. Only the total participants had statistically significant ORs in the third and fourth SUA level, which supported a possible threshold effect in the relationship between hyperuricemia and risk of CVD among hypertensive patients.

Hyperuricemia was positively associated with CVD in hypertensive males and females when a unified cut-off of SUA level 7 mg/dl was used (OR 1.34 for females; OR 1.28 for males) (Figure 1). However, the ORs of hyperuricemia for all CVD were greater in magnitude in hypertensive women than in men when patients had co-morbid diabe-

Table 5. Quartiles of uric acid level and risk of cardiovascular events, by sex

Odds ratio (95% C.I.)	≤ 5.0 mg/dl n = 765 (22.52%)	5.1-7.0 mg/dl n = 1,572 (46.28%)	7.1-9.0 mg/dl n = 838 (24.67%)	> 9.0 mg/dl n = 222 (6.54%)
Total	1 (Reference)	1.02 (0.85-1.21)	1.44 (1.18-1.76)*	1.55 (1.15-2.09)*
Men	1	0.92 (0.69-1.21)	1.18 (0.88-1.59)	1.28 (0.86-1.90)
Women	1	0.96 (0.76-1.21)	1.32 (0.98-1.76)	1.28 (0.77-2.16)

* Statistically significant (p < 0.05).

tes. The ORs of all CVD in this diabetes sub-group were statistically significantly only in females (p = 0.01 for females; p = 0.07 for males). Sub-group analyses demonstrated the hyperuricemia had significant risk only in females when hypertension had co-morbid diabetes.

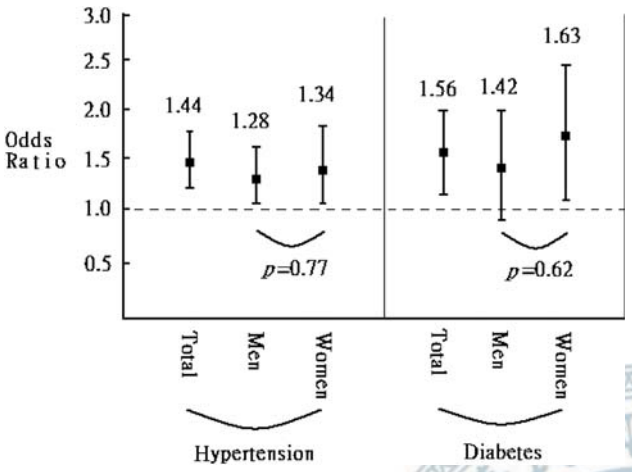

Figure 1. *Odds ratios (ORs) of hyperuricemia (SUA level > 7 mg/dl) on cardiovascular disease for patients with hypertension and diabetes, by sex. The degrees of association between hyperuricemia and CVD are shown with p values. Bars show the 95% confidence interval. CVD, cardiovascular disease; SUA, serum uric acid.*

In clinical practice, hyperuricemia was defined as SUA levels > 7.0 mg/dl, the same as the cut-off value of the present study (Figure 1). Although the ORs and p values were all statistically insignificant in both sexes when four quartiles of SUA levels were used (Table 5), these became statistically significant in both sexes when two quartiles of SUA level were used (Figure 1). Again, this supported a possible threshold effect in the relationship between hyperuricemia and risk of CVD among hypertensive patients.

Hyperuricemia in essential hypertensive Taiwanese patients has been associated with increased CVD risk in univariate analysis. However, by multivariate analysis, these results imply that hyperuricemia did not confer an increased risk of CVD (Table 6).

DISCUSSION

Patients with hyperuricemia, often accompanied by the various parameters of metabolic syndrome,[10] and higher SUA values in men are associated with an increasing number of MS components, and more fre-

Table 6. Odds ratios (ORs) of traditional risk factor on cardiovascular disease by univariate or multivariate analysis (with p values)

CV risk	Odds ratio	95% C.I.	p value
Univariate analysis			
Serum uric acid	1.07	(1.03,1.11)	< 0.001
Sex (Male vs. Female)	1.74	(1.52,1.99)	< 0.001
Waist circumference	1.02	(1.01,1.03)	< 0.001
BMI	1.01	(0.99,1.03)	0.37
Age	1.03	(1.02,1.04)	< 0.001
Smoking	1.49	(1.22,1.81)	< 0.001
History of hypertension > 5 year	1.15	(1.01,1.32)	0.04
Hypercholesterolemia	0.59	(0.46,0.75)	< 0.001
Hypertriglycemia	0.98	(0.77,1.25)	0.89
Diabetes mellitus	1.38	(1.20,1.60)	< 0.001
Multivariate analysis			
Serum uric acid	1.03	(1.00,1.07)	0.07
Sex (male vs. female)	1.40	(1.19,1.66)	< 0.001
Waist circumference	1.01	(1.00,1.02)	0.07
Age	1.03	(1.01,1.04)	< 0.001
Smoking	1.29	(1.03,1.63)	0.03
History of hypertension > 5 year	1.12	(0.96,1.30)	0.17
Hypercholesterolemia	0.67	(0.52,0.86)	0.002
Diabetes mellitus	1.28	(1.09,1.51)	0.003

* Statistically significant (p < 0.05). BMI, body mass index; C.I., confidence interval; CV, cardiovascular.

quently, to MS itself (p = 0.006).[11] Hyperuricemia has been associated with an increased risk of cardiovascular events in some, but not all, studies. However, whether an elevation of SUA is an independent cardiovascular risk factor or whether hyperuricemia has prognostic value in the specific setting of essential hypertension remains controversial.

The present study has been designed to determine the association of SUA with the risk of CVD after controlling for the traditional group of established risk factors by multivariate analyses in a large cohort of Taiwanese men and women with essential hypertension.

The data here reveals that hyperuricemia is positively associated with CVD in hypertensive women and men when a unified cut-off of SUA > 7 mg/dl was used (Figure 1). In all of the study participants, those with hyperuricemia had 1.44-fold greater risk for CVD than non-hyperuricemic patients. The ORs of hyperuricemia for all CVD were greater in magnitude in hypertensive females than in males when patients had co-morbid diabetes, and the ORs of all CVD in the diabetes sub-group were statistically significant only in females (p = 0.01 for females, p = 0.07 for males). The final analysis demonstrated that hyperuricemia in essential hypertensive Taiwanese patients is associated with increased risk of CVD in univariate analysis, but not in multivariate analysis.

A previous study by Johan reported that SUA level is an independent predictor of hypertension incidence and longitudinal blood pressure progression.[12] Elevated SUA concentration post-stroke is predictive of subsequent cardiac death, and independent of conventional risk factors and of renal function or diuretic use.[13] Several large studies have identified elevated SUA concentration as a predictor of cardiovascular events like myocardial infarction.[6] Other data suggest that hyperuricemia has a continuous, independent, specific, and significantly positive relationship to cardiovascular mortality in the general population, and is independent of diuretic use, cardiovascular risk status, or menopausal status.[6,14-16] These aforementioned reports demonstrate the role of SUA as an independent, modifiable marker of CVD among Caucasians.

The present Taiwanese study demonstrates a non-independent association between hyperuricemia and CVD after full adjustment by a multivariate analysis. Ethnic variations may be the possible reason. Among Asian countries, relatively higher cerebral-vascular stroke and lower coronary heart event rates have been reported.[17] A high prevalence of hyperuricemia in hypertensive subjects in Taiwan has also been reported, with a mean of 35% in males, and 43% in females.[18] The genetic, different lifestyles, or environmental components presumably contribute to the differences. Thus, the present study also investigates possible differences in ethnic groups to explore the role of hyperuricemia in cardiovascular complications, especial in Taiwanese subjects.

Is hyperuricemia a marker for some kind of pathophysiologic process that accelerates CVD? The mechanisms are not fully known and there are several different complex factors affecting the progressive course of CVD. Endothelial dysfunction is a hallmark of metabolic syndrome and its serial complication. Some studies suggest the pathologic role of hyperuricemia is associated with deleterious effects on endothelial function, as an explanation for insulin resistance.[19] And elevated SUA levels dose-dependently reduced the vasodilation of aortic artery rings to acetylcholine, demonstrating that SUA can inhibit endothelial response. Moreover, SUA potently decreases endothelial nitric oxide (NO) bioavailability in both cell culture and in experimental models of animal study.[20]

Reducing endothelial NO levels is a known mechanism for inducing insulin resistance.[21] This is due to inhibition of insulin action, as insulin stimulates glucose uptake in skeletal muscle by increased blood flow to these tissues through a NO-dependent pathway. In this scenario, allopurinol or benzbromarone administration in hyperuricemic patients may improve endothelial function and reduce ischemia, and further act to prevent metabolic syndrome by blocking hyperuricemia-induced endothelial dysfunction. Aside from blocking uric acid, allopurinol also blocks oxidant formation and can reverse the impaired endothelial NO production in both congestive heart failure and type 2 diabetes population.[22] The effect correlates with the reduction of SUA level and improvement in flow-mediated brachial artery vasodilatation, a measure of in vivo vascular NO activity.[23]

Another potential mechanism of SUA for CVD may be mediating the systemic inflammatory reaction that may affect the cardiovascular system. Soluble uric acid is

pro-inflammatory and stimulates the production of chemokines from vascular smooth muscle cells and cytokines from leukocytes. Concentrations of SUA are positively correlated with high-sensitivity C-reactive protein, the factor related to circulating inflammatory markers. SUA can also induce the synthesis of monocyte chemo-attractant protein-1 in rat vascular smooth muscle cells,[24] which is an important chemokine in atherosclerosis and CVD. Hyperuricemia also increases platelet adhesiveness, increases platelet lysis, and stimulates thrombus formation.[25] Platelet dysfunction may also reflect endothelial dysfunction in these patients. Thus, based on these studies, SUA may have the ability to promote inflammation and damage vascular systems that may consequently accelerate the atherosclerotic process and the development of CVD.

Another interesting issue is the difference between the sexes. The correlation observed between SUA and CVD in females did not confirm results from previous studies.[9] The ORs of hyperuricemia for all CVD were greater in magnitude in hypertensive females than in males only when patients had co-morbid diabetes (Figure 1). Previously, Kuo-Liong Chien demonstrated that the risk of stroke events related to hyperuricemia appears to be stronger in females than in males.[15] The Framingham cohort also report a linear trend of hazard risks among females.[26] The positive correlation between hyperuricemia and age is also demonstrated in females in the National Health and Nutrition Examination Survey (NHANES) I study.[6] Moreover, in the LIFE study, baseline SUA was significantly associated with increased development of the primary end-point of cardiovascular death, stroke, or MI, even after adjustments for traditional cardiovascular risk factors in females, but not in males.[27] However, the results of our study are not consistent with previous reports.

The positive correlation between BMI and hyperuricemia has also been well-established.[4] Results of the present study are inconsistent in this regard. BMI and waist circumference are statistically insignificant. In obese patients, decreased urinary uric acid clearance may play a role in the elevation of SUA level. Yamashita et al. illustrated that uric acid clearance increased when BMI was reduced.[28] The correlation of the present data between waist circumference and hyperuricemia is inconsistent with previous studies, although such finding needs to be interpreted with some caution because of the small number of patients in the obese sub-group (BMI $\geq$ 30 kg/m^2). Among Asian countries, BMI is relatively lower in the general population. Therefore, ethnic variation also may be a possible explanation.

Strengths and limitations

The primary design structure of the present study included its cross-sectional study and lack of long-term follow-up. Nonetheless, there are several limitations. First, we included middle-to-old aged Taiwanese professionals as our sample of Chinese ethnicity. As such, the generalizability to other ethnicities or younger populations may be limited. Second, routine screening imaging of the brain was not performed in this study. Thus, it is possible that asymptomatic cases of stroke may have gone undetected. If anything, the results therefore may underestimate the true risk associated with hyperuricemia. Third, as with any cross-sectional study, the causal relationships between SUA concentration and CVD cannot be evaluated. Fourth, the data cannot invoke a particular mechanism. Lastly, other potential influences, such as dietary habits, income and social status, were not examined.

CONCLUSIONS

Hyperuricemia in essential hypertensive Taiwanese patients is associated with increased risk of CVD in univariate analysis, but is statistically insignificant after multivariate analysis. Thus, hyperuricemia may be associated with increased risk of CVD but not an independent risk factor of CVD in essential hypertensive Taiwanese patients. Hyperuricemia might be viewed as a signal of underlying alterations. Nonetheless, future prospective studies are required to fully determine the nature of the causal relationship between SUA and the development of CVD, and to definitively address whether lowering SUA is beneficial in preventing CVD.

CONFLICT OF INTEREST

The authors have no conflicts of interest directly relevant to the contents of this article.

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