Hypertension Was the Major Risk Factor Leading to Development of Cardiovascular Diseases Among Men with Hyperuricemia

KUAN-CHIA LIN, HSUAN-MING TSAO, CHEN-HUAN CHEN, and PESUS CHOU

ABSTRACT. ***Objective***. A 7-year followup study among men with hyperuricemia was conducted to study the longterm relationships between serum uric acid concentrations and cardiovascular diseases. Any interaction between uric acid levels and other risk factors (e.g., obesity, hypertension) on the development of cardiovascular diseases was also examined.

Methods. A total of 391 men with hyperuricemia aged 30 and over screened from the community-based Kinmen study in 1991-92 (the baseline study) were followed in 1997-98, with a 75% followup rate. Demographic, clinical, and biochemical data were collected in both baseline and followup periods.

Results. After followup for 7 years, the significant risk factors of coronary heart disease were age, increase of uric acid level at followup, baseline systolic blood pressure, and increase of systolic blood pressure at followup. Factors independently associated with left ventricular hypertrophy included baseline systolic blood pressure and increase of systolic blood pressure at followup. Gouty syndrome, age, baseline fasting plasma glucose level, and increase of systolic blood pressure followup were significantly related to cardiac arrhythmia. After adjusting for baseline serum uric acid level, we found that hyperuricemic men with hypertension, especially overt hypertension stage 2 and stage 3, would predict cardiovascular disease incidence synergistically with uric acid level.

Conclusion. There is a positive and statistically significant relationship between gout and subsequent cardiac arrhythmia. Moreover, hypertension was the major risk factor leading to aggravation of development of atherosclerosis among hyperuricemic subjects. Gout and elevated uric acid level seemed not to be an independent risk factor for most cardiovascular diseases. Nevertheless, blood pressure level was predictive for cardiovascular disease incidence synergistically with serum uric acid level. (J Rheumatol 2004;31:1152–8)

Key Indexing Terms:
HYPERURICEMIA HYPERTENSION CARDIOVASCULAR DISEASES

Concentrations of serum uric acid, the end-product of purine metabolism, are frequently elevated in patients with hypertension or ischemic heart disease[1-3]. The role of uric acid in the development of cardiovascular diseases (CVD), however, remains uncertain, as numerous characteristics can confound the observed associations[4-7].

In recent years the debate has intensified as a result of renewed interest in identifying uric acid-treatable targets for the prevention of coronary heart disease, and in light of several new studies with seemingly conflicting results[8-10]. Major viewpoints suggest it is possible that the relation between uric acid and CVD is mediated entirely through other risk factors; there are also several potential mechanisms whereby uric acid could exert a direct effect in promoting atherogenesis or in adversely affecting the clinical manifestations of patients with established atherosclerosis.

The hypothesis of hyperuricemia as a risk factor for CVD has recently been suggested; high uric acid levels were shown to stabilize platelet aggregation and enhance thrombotic tendency[11-14]. On the other hand, it has been well documented that uric acid levels correlate with many of the traditional and some of the more recently identified cardiovascular risk factors, including older age, male sex, hypertension, diabetes mellitus, hypertriglyceridemia, obesity, and the insulin-resistance/hyperinsulinemia syndrome[4–7,15,16]. In addition, uric acid levels increase as renal function declines.

These relations suggest that the observed association between uric acid levels and CVD may represent an epiphenomenon, reflecting the complex interaction between uric acid and other risk factors. At the same time, they greatly confound efforts to establish the "independence" of uric

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acid as a cardiovascular risk factor using conventional statistical techniques.

We followed 391 hyperuricemic men found in the Kinmen community-based study in 1991-92 from 1997 to 1998 with structured interviews and examinations by the Community Medicine Research Center, National Yang-Ming University[17,18]. Our aim was to explore the longterm relationships between serum uric acid concentrations and CVD. We investigated whether an interaction exists between uric acid concentrations and other risk factors (e.g., obesity, hypertension) in the development of CVD.

MATERIALS AND METHODS

Study subjects. The Kinmen study is a population survey and has been conducted since 1991. The population of Kinmen, a group of islands lying very close to southern mainland China, has been the focus of a number of population-based studies[17-25] conducted by the Yang-Ming Crusade, a research effort organized by the medical students of National Yang-Ming University[26]. The characteristics of the target population and the methodology have been reported[26,27]. In 1991-92, a baseline survey was conducted in 3185 registered residents (1515 men, 1670 women) over 30 years of age in Kin-Hu (a major town of Kinmen). The prevalence of hyperuricemia (uric acid ≥ 7.0 mg/dl) in men was found to be 25.8% (391/1515)[17]. We then followed 391 hyperuricemic men in 1997-98 to study the incidence of CVD and associated disorders. Demographic and clinical data including body mass index (weight/height^2), smoking habit, drinking habit, verification of personal and family disease history, and systolic and diastolic blood pressure (averaged from 3 readings separated by at least 5 min) were measured and documented during face-to-face interviews by the Yang-Ming Crusade using structured questionnaires in both baseline and followup studies.

Overnight fasting blood samples were drawn for plasma glucose, serum uric acid, lipid, and other biochemical measurements. Blood samples were preserved with EDTA in NaF tubes, kept frozen (–20°C), and were sent to the biochemical laboratory of Taipei Veterans General Hospital-Taipei for testing. Uric acid levels were determined using the enzymatic spectrophotometric method (reagent kits by bioMérieux, Chardonnieres-les-Dains, France). Plasma glucose concentration was determined using the hexokinase glucose-6-phosphate dehydrogenase method with glucose (reagent kits by Gilford, Oberlin, OH, USA). Serum total cholesterol and triglyceride were analyzed using the cholesterol oxidase-peroxidase method (T-CHO kit, Denka Seiken, Tokyo, Japan) and the glycerokinase-glycerophosphate-oxidase-peroxidase method (RM1575-K Cleantech TG-S reagent kit, Iatron, Tokyo, Japan). Serum high density lipoprotein-cholesterol (HDL-C) was measured using the precipitation method with the Kodak Ektachem HDL cholesterol kit.

Classification of CVD. CVD were predominately diagnosed by a senior cardiologist based on individual electrocardiograph and clinical examination[28,29]. After individual structured examination, 4 major types of CVD were investigated.

Coronary heart diseases: including acute/recent myocardial infarction, old myocardial infarction (pathological Q wave), ischemic ST-segment change (horizontal or downsloping ST segment depression with or without T wave inversion).

Left ventricular hypertrophy: by QRS voltage criteria of precordial leads (sum of the R wave in lead V5, V6, and the S wave in lead V1 > 35 mm in adults older than 30 years; or the sum of the maximal R and the deepest S wave in the precordial leads > 45 mm; or amplitude of the R wave in lead V5 > 26 mm; or amplitude of the R wave in lead V6 > 20 mm) and limb leads (sum of the R wave in lead I and S wave in lead II is ≥ 26 mm or amplitude of R wave in lead I ≥ 14 mm; or S wave in lead aVR is ≥ 15 mm; or R wave in lead aVL ≥ 12 mm).

Cardiac arrhythmia: including atrial fibrillation/flutter, supraventricular tachycardia, premature atrial beats, and premature ventricular beats. Conduction disturbances: including first-degree atrioventricular (AV) block (PR interval > 200 ms), Morbitz type I and 2 second-degree AV block, complete AV block, right bundle branch block, and left bundle branch block.

Definition of variables. Hyperuricemia was defined as uric acid ≥ 7.0 mg/dl for men in this followup study[30,31]. Gout was clinically diagnosed by a senior rheumatologist based on established criteria from history taking, clinical record review, and individual physical examination[32]. Three consecutive blood pressure readings at least 5 min apart were taken from the right arm with the person seated. Diastolic blood pressure was measured at the fifth phase. Hypertension was defined if the average of the 3 readings was ≥ 140/90 mm Hg[33].

Statistical analysis. According to the development of CVD, study subjects were divided into Group 1 (subjects with coronary heart disease in followup periods), Group 2 (subjects with left ventricular hypertrophy in followup periods), Group 3 (subjects with cardiac arrhythmia in followup periods), Group 4 (subjects with conduction disturbance in followup periods), and the reference group (subjects with persistent asymptomatic hyeruricemia in both baseline and followup periods). The differences in study variables among the 5 groups were tested at baseline and in the followup period. Mann-Whitney U test (in view of the non-normal distribution of the results) and chi-square test (no case number of units in chi-square cell had expected count < 5) were used, as appropriate, to analyze group differences. The 7-year cumulative incidence (CI, %) of each CVD was analyzed separately for old and young hyperuricemic men for comparison. To analyze the independent effect and the influence of variable changes between 2 data points on the development of CVD, a multiple logistic regression including the absolute change of each variable was assessed in order to adjust the initial value. All statistics were analyzed by the Statistical Analysis System (SAS).

RESULTS

In 1997-98, 391 men with hyperuricemia (including 30 gout cases and 361 asymptomatic subjects) without any CVD at baseline were followed and had complete reexamination data with 75% followup rate (293/391). Any treatment in any subjects for CVD or use of diuretics for hypertension was excluded in data analysis. The reasons for dropouts included known treatment for CVD or use of diuretics at baseline (n = 39), death (n = 16), changing residence or migration (n = 31), and serious disability (n = 12). As there were no significant differences in uric acid concentration and other risk profiles at baseline between respondents and nonrespondents, loss to followup bias would not be considered important.

Table 1 shows the 7-year cumulative incidence of each CVD among men with hyperuricemia from baseline to followup periods (results with the chi-square test). Subjects with older age seemed to have higher incidence rate of coronary heart disease (12.5%) and cardiac arrhythmia (14.84%) than younger subjects (3.63% and 2.42%, respectively). On the other hand, the difference between the 2 age groups regarding the incidence rate of left ventricular hypertrophy and conduction disturbance was not statistically significant.

Table 2 presents the baseline characteristic of risk profiles among men with hyperuricemia stratified by followup CVD status (where category data were tested by

Table 1. The 7 year cumulative incidence (%) of cardiovascular diseases among hyperuricemic men from baseline (1991–92) to followup (1997–98) in Kin-Hu, Kinmen.

Cardiovascular Diseases	Baseline age < 50 yrs, n = 165	Baseline age ≥ 50 yrs, n = 128	p
Coronary heart disease	3.63 (6/165)	12.5 (16/128)	0.021
Left ventricular hypertrophy	33.93 (56/165)	39.06 (50/128)	0.407
Cardiac arrhythmia	2.42 (4/165)	14.84 (19/128)	0.009
Conduction disturbance	9.09 (15/165)	15.62 (20/128)	0.188

the chi-square test, and all continuous statistical inference by Mann-Whitney U test). The results indicated that Group 1 subjects (with coronary heart disease in followup periods) were older and had higher values for blood pressure, serum uric acid, plasma creatinine, and blood urea nitrogen. Group 2 subjects (with left ventricular hypertrophy in followup periods) were particularly obese and had higher systolic blood pressure. For Group 3 (subjects with cardiac arrhythmia in followup periods), characteristics were found in subjects with older age, high blood pressure, more gouty attacks, and hyperglycemia. Compared with the reference group of men [those with persistent asymptomatic hyperuricemia in both baseline and followup periods (Group 5)], subjects with conduction disturbance in followup periods (Group 4) had no significant difference of baseline characteristics.

After 7-year followup, the characteristics of risk profiles were somewhat different from baseline in each group (Table 3; categorical data tested by chi-square test, and all continuous statistical inferences by Mann-Whitney U test). First, Group 1 had higher incidence of gout, higher systolic blood pressure, and higher serum creatinine during followup. Group 2 still had significantly higher blood pressure and body mass index. In addition, Group 3 had higher incidence of gout and hyperglycemia. However, there was no further significant difference in serum uric acid level among these study groups including the reference group.

To study the factors independently related to the development of CVD and to integrate the baseline and followup data, we conducted logistic regressions (Table 4) for the correlates of coronary heart disease (model 1), left ventricular hypertrophy (model 2), and cardiac arrhythmia (model 3), assessing the effect of risk profile change during 7-year followup. The significant correlates of coronary heart disease were age, increase in uric acid level during followup, baseline systolic blood pressure, and increase in systolic blood pressure during followup. Factors significantly associated with left ventricular hypertrophy included baseline systolic blood pressure and increased systolic blood pressure during followup. In model 3, gouty syndrome, age, baseline fasting plasma glucose level, and increased systolic blood pressure during followup were significantly related to cardiac arrhythmia. The association between gout and cardiac arrhythmia remained statistically significant after adjusting for age.

Because all study subjects screened from the Kinmen community-based study in 1991-92 (baseline study) were hyperuricemic subjects (uric acid ≥ 7.0 mg/dl), in order to

Table 2. Baseline characteristic of risk profiles among hyperuricemic men in Kin-Hu, Kinmen, stratified by cardiovascular disease status during followup.

Variable	Baseline in 1991–92							
	Group 1[a] (n = 32)	Group 2[b] (n = 106)	Group 3[c] (n = 23)	Group 4[d] (n = 35)	Group 5[e] (n = 142)	p (a vs e)	p (b vs e)	p (c vs e)
Age, yrs	56.54 ± 8.12	49.78 ± 10.47	56.27 ± 9.42	51.84 ± 11.65	46.87 ± 10.13	< 0.001	0.067	0.002
Uric acid, mg/dl	8.33 ± 0.89	7.97 ± 0.87	8.22 ± 0.91	8.21 ± 1.15	7.82 ± 0.76	0.033	0.224	0.107
Gout, %	15.62	12.26	26.00	11.43	8.45	0.318	0.429	0.042
Alcohol consumption, %	37.50	50.94	39.13	42.85	39.43	0.628	0.225	0.601
Systolic blood pressure, mm Hg	144.87 ± 22.67	140.37 ± 23.52	144.39 ± 23.41	141.58 ± 22.91	130.83 ± 17.23	0.024	0.002	0.016
Diastolic blood pressure, mm Hg	89.07 ± 10.68	85.33 ± 12.67	88.73 ± 16.05	89.43 ± 11.65	81.92 ± 12.87	0.058	0.083	0.104
Smoker, %	65.62	41.51	60.86	48.57	42.25	0.072	0.201	0.158
Body mass index, kg/m^2	23.28 ± 3.49	23.39 ± 2.46	24.54 ± 3.07	24.62 ± 2.76	24.29 ± 2.87	0.198	0.012	0.675
Fasting plasma glucose, mg/dl	98.46 ± 10.17	102.80 ± 16.88	112.36 ± 23.63	99.37 ± 13.23	99.43 ± 17.53	0.733	0.191	0.026
Triglyceride, mg/dl	126.46 ± 70.76	115.45 ± 68.97	124.63 ± 81.41	129.56 ± 83.61	120.55 ± 64.16	0.781	0.218	0.531
Total cholesterol, mg/dl	221.02 ± 36.28	211.77 ± 37.03	195.36 ± 22.65	226.08 ± 35.48	215.02 ± 33.50	0.548	0.532	0.069
HDL-C, mg/dl	51.86 ± 16.09	51.95 ± 15.83	46.40 ± 14.18	51.44 ± 12.53	49.68 ± 12.19	0.392	0.052	0.742
Creatinine, mg/dl	1.06 ± 0.18	0.95 ± 0.24	0.90 ± 0.15	0.94 ± 0.12	0.96 ± 0.16	0.043	0.781	0.244
Blood urea nitrogen, mg/dl	18.53 ± 2.56	17.22 ± 3.01	17.27 ± 3.19	18.52 ± 3.55	17.20 ± 3.92	0.025	0.884	0.850

[a] Subjects with coronary heart disease during followup period. [b] Subjects with left ventricular hypertrophy during followup period. [c] Subjects with cardiac arrhythmia during followup period. [d] Subjects with conduction disturbance during followup period. [e] Subjects with persistent asymptomatic hyperuricemia in both baseline and followup period. HDL-C: high density lipoprotein cholesterol.

Table 3. Followup characteristic of risk profiles among hyperuricemic men in Kin-Hu, Kinmen, stratified by cardiovascular disease status during followup.

Variable	Followup in 1998–99 Group 1[a] (n = 32)	Group 2[b] (n = 106)	Group 3[c] (n = 23)	Group 4[d] (n = 35)	Group 5[e] (n = 142)	p (a vs e)	p (b vs e)	p (c vs e)
Uric acid, mg/dl	8.78 ± 1.39	8.02 ± 1.37	7.83 ± 2.18	8.27 ± 1.56	8.08 ± 1.51	0.210	0.482	0.602
Gout, %	40.62	30.18	39.13	31.42	19.71	0.035	0.107	0.041
Alcohol consumption, %	34.37	31.13	30.43	25.71	35.21	0.662	0.287	0.192
Systolic blood pressure, mm Hg	165.54 ± 35.26	145.98 ± 24.66	143.22 ± 24.32	141.43 ± 24.73	134.79 ± 16.50	0.018	0.001	0.217
Diastolic blood pressure, mm Hg	99.64 ± 2.66	95.47 ± 16.78	91.66 ± 11.44	89.95 ± 14.62	88.92 ± 13.33	0.146	0.022	0.583
Smoker, %	18.75	17.92	21.73	28.57	28.16	0.128	0.083	0.663
Body mass index, kg/m^2	24.42 ± 4.13	24.02 ± 3.04	24.64 ± 2.43	24.62 ± 2.85	25.67 ± 3.14	0.311	0.001	0.294
Fasting plasma glucose, mg/dl	112.36 ± 32.26	102.48 ± 29.46	120.77 ± 32.13	101.75 ± 31.85	99.95 ± 27.73	0.259	0.573	0.041
Triglyceride, mg/dl	114.54 ± 42.31	118.26 ± 56.57	125.72 ± 61.29	128.41 ± 83.61	119.39 ± 71.14	0.260	0.823	0.187
Total cholesterol, mg/dl	179.91 ± 26.53	181.18 ± 37.16	176.44 ± 34.20	188.66 ± 37.62	180.13 ± 33.66	0.723	0.752	0.125
HDL-C, mg/dl	46.91 ± 12.74	46.69 ± 13.18	40.50 ± 19.93	42.10 ± 10.08	42.53 ± 11.12	0.227	0.038	0.646
Creatinine, mg/dl	1.26 ± 0.28	1.08 ± 0.19	1.04 ± 0.19	1.16 ± 0.14	1.09 ± 0.15	0.034	0.509	0.533
Blood urea nitrogen, mg/dl	19.45 ± 3.44	17.27 ± 3.04	18.01 ± 3.27	18.87 ± 3.84	17.78 ± 4.17	0.161	0.441	0.893

[a] Subjects with coronary heart disease during followup period. [b] Subjects with left ventricular hypertrophy during followup period. [c] Subjects with cardiac arrhythmia during followup period. [d] Subjects with conduction disturbance during followup period. [e] Subjects with persistent asymptomatic hyperuricemia in both baseline and followup period. HDL-C: high density lipoprotein cholesterol.

Table 4. Logistic regression of cardiovascular diseases among hyperuricemic men in Kin-Hu, Kinmen. Assessment of the impact of risk profile change during 7-year followup. Initial independent variables: age, uric acid, body mass index, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, serum creatinine, gouty arthritis, triglyceride, alcohol consumption, smoking, total cholesterol, blood urea nitrogen, and high density lipoprotein cholesterol.

Variable	Coronary Heart Disease (yes vs no) OR	95% CI	Left Ventricular Hypertrophy (yes vs no) OR	95% CI	Cardiac Arrhythmia (yes vs no) OR	95% CI
Age, yrs	1.12	1.03–1.20	NS	NS	1.08	1.02–1.17
Uric acid, mg/dl, baseline	NS	NS	NS	NS	NS	NS
Uric acid, each 1 mg/dl increase during followup	1.19	1.12–4.03	NS	NS	NS	NS
Systolic blood pressure, mm Hg, baseline	1.04	1.01–1.07	1.04	1.02–1.06	1.03	1.01–1.09
Systolic blood pressure, each 1 mm Hg increase during followup	1.05	1.02–1.08	1.03	1.01–1.05	NS	NS
Body mass index, kg/m^2, baseline	NS	NS	NS	NS	NS	NS
Body mass index, each 1 kg/m^2 increase during followup	NS	NS	NS	NS	NS	NS
Fasting plasma glucose, mg/dl, baseline	NS	NS	NS	NS	1.16	1.05–1.32
Gout, yes vs no	NS	NS	NS	NS	3.09	1.21–16.86

NS: Not significant.

analyze the interaction between degree of hypertension and uric acid level in the 7-year incidence of major CVD among hyperuricemic men, we then utilized a uric acid level of 8 mg/dl as a relative upper limit of the degree of hyperuricemia. Figure 1 displays the interaction between degree of hypertension and uric acid level in the 7-year incidence of major CVD among hyperuricemic men, after adjustment for baseline serum uric acid level. The results revealed that hyperuricemic men with hypertension, especially overt hypertension stage 2 and stage 3, predicted CVD incidence synergistically with uric acid level (overall p = 0.002 for chi-square test).

DISCUSSION

The major findings of this followup study were: (1) The positive and statistically significant relationship between gout and subsequent cardiac arrhythmia. (2) Most CVD in hyperuricemic men were predominately determined by baseline blood pressure level, particularly the systolic value; and risk paralleled persistently increased blood pressure level. (3) The "independence" of gout and elevated uric acid concentration as a risk factor for CVD cannot be confirmed. (4) The role of hypertension in predicting CVD incidence in hyperuricemic men was synergistic with uric acid concentration.

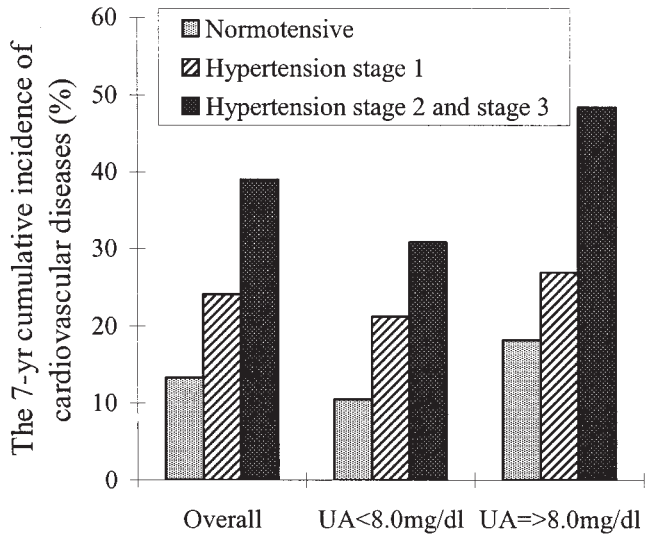

Figure 1. The 7-year cumulative incidence (%) of CVD (including coronary heart disease, cardiac arrhythmia, and conduction disturbance) stratified by hypertension status among men with hyperuricemia from 1991-92 (baseline) to 1998-99 (followup period). Hyperuricemic men with hypertension, especially overt hypertension stage 2 and stage 3, predicted CVD incidence synergistic with uric acid (UA) level (overall p = 0.002, chi-square test).

Serum uric acid is the main end-product of purine metabolism[34,35]. Purines are nucleotide compounds derived in the human body from 3 sources: dietary, *de novo* biosynthesis, and from the breakdown of tissue nucleic acids. The presence of hyperuricemia indicates that physiologic homeostasis has been altered by increases in endogenous production or ingestion, or by decreases in excretion of monosodium urate, which is the metabolic end-product of purine degradation. Although hyperuricemia is generally accepted as the primary risk factor for the development of gout, many hyperuricemic subjects are asymptomatic[17,18,36,37]. In contrast with gout, the importance of asymptomatic hyperuricemia remains uncertain in the general population[38,39]: unless the gouty symptom occurs, people with hyperuricemia usually remain unaware of subsequent complications such as hypertension, coronary heart disease, renal disease, and diabetes. Recent reports from many epidemiologic studies have discussed the specific relationship between uric acid concentration itself and the development of CVD[3-16]. Their conclusions include: that the relation between serum uric acid and CVD is mediated entirely through other risk factors[4-7,15,16]; or that there are also several potential mechanisms whereby uric acid could exert a direct effect in promoting atherogenesis; or that serum uric acid concentration adversely affects the clinical manifestations of patients with established atherosclerosis[10-14].

In our study, hyperuricemic men who converted to CVD after 7-year followup were older and more obese, with higher serum creatinine, hyperlipidemia, hypertension, and gouty attack. However, after using multiple regression to explore the independent risk factor, we found these major CVD were predominately determined by baseline blood pressure levels, particularly the systolic value; moreover, the risk paralleled a persistently increased level of blood pressure. This suggests that hypertension was the major risk factor leading to aggravation of the development of atherosclerosis among hyperuricemic subjects even though no gouty arthritis attack occurred. The question, then, is whether uric acid is causally related to atherosclerosis, or if it merely serves as a readily identifiable serum marker for other, more fundamental risk factors. Based on the logical basis of multivariate refutation (based on 5% type I error), our study findings suggest that the observed association between uric acid levels and CVD may represent an epiphenomenon, reflecting the complex interaction between uric acid and hypertension or the insulin-resistance/hyperinsulinemia syndrome.

Previous studies have suggested a potential role of uric acid for CVD as a mediator for the development of other risk factors, particularly systemic hypertension[1,4,5,11]. Although hyperuricemia and hypertension are clearly linked, the mechanisms underlying this relationship are uncertain. Whereas hypertensive renal dysfunction could account for increased uric acid concentrations[1,2,40-42], it is also conceivable that hyperuricemia itself may predispose to the development of hypertension or play a role either in the rate of blood pressure progression or in the effects of hypertension on other organs, including the kidney, heart, brain, or vascular endothelium. Indeed, there have been at least 2 studies implicating uric acid as a risk factor for incident hypertension[43,44]. On the other hand, our findings demonstrated a positive and statistically significant relationship between gout and subsequent cardiac arrhythmia. Although the exact mechanism is not clear, hyperuricemia was reported to be associated with the more ventricular extrasystoles in 2 studies of treatment in hypertensive patients[45,46]. In addition, uric acid infusion augments the occurrence of ventricular tachyarrhythmias in the ischemic heart of a rabbit disease model[47]. These results imply that better identification and treatment or prevention of gout would be beneficial in the prevention of a subset of cardiac arrhythmias. However, this logical basis of multivariate refutation should be tested in different racial studies, since findings on a link between gout and arrhythmic events are still not consistent and merit further evaluation.

The independent and specific association of elevated serum uric acid with CVD could not be elucidated in our study, since increasing serum uric acid concentration was only slightly associated with the development of coronary heart disease. Nevertheless, it was more interesting to find that hypertension predicted CVD incidence and interacted synergistically with serum uric acid level. This suggests

that hyperuricemia and persistently increased serum uric acid levels coexisting in hypertensive subjects may subsequently enhance the risk factor value of hypertension, leading to aggravation of development of atherosclerosis and its sequellae[10,48].

Indeed, apart from the interactions between uric acid and other risk factors, there are several plausible mechanisms whereby uric acid may have a direct effect on atherogenesis or on the clinical course of CVD. First, there is evidence that increased uric acid levels promote oxygenation of low density lipoprotein cholesterol and facilitate lipid peroxidation[12]. In addition, increased uric acid levels are associated with increased production of oxygen free radicals, and each of these factors is known to play a pivotal role in the progression of atherosclerosis[13,14]. Moreover, it has been suggested that elevated uric acid levels are associated with increased platelet adhesiveness, and this effect could potentiate thrombus formation in patients with acute coronary syndromes[11].

However, evidence of an association of elevated serum uric acid with CVD incidence or mortality is still inconsistent in recent and previous epidemiologic studies, and a causal relationship remains controversial. Our study with repeated followup measurement had the methodological advantage of clarifying the longterm variation of serum uric acid changes; moreover, based on the previous findings, we favor the viewpoint that serum uric acid concentration itself may contribute to the increased risk of atherosclerosis in those with severe hypertension. High serum uric acid levels may adversely affect the clinical manifestations of patients with established atherosclerosis. Previous research has reported similar results: stroke in patients with type 2 diabetes mellitus was independently predicted by hyperuricemia[48].

Several possible limitations of this study should be considered in interpreting the results. There was probably misclassification of electrocardiographic diagnosis for CVD, but this may derive from non-differential misclassification bias leading to underestimation of risk, so the real effect may be stronger. Further, although the followup rate was 75%, there were no significant differences in uric acid concentration and other risk profiles at baseline between respondents and nonrespondents. Selection bias due to nonresponse was negligible.

Our findings particularly demonstrated the positive and statistically significant relationship between gout and subsequent cardiac arrhythmia. Besides this, in consideration of most cardiovascular events in our study, hypertension was the major risk factor leading to aggravation of the development of atherosclerosis among hyperuricemic subjects. Gout and elevated uric acid concentration itself seemed not to be independent risk factors for most CVD. Nevertheless, blood pressure level predicted cardiovascular disease incidence synergistically with serum uric acid concentration.

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