THE SERUM URIC ACID AND RELATED CARDIOVASCULAR RISK FACTORS IN SOUTH TAIWAN

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Abstract. Hyperuricemia has been shown to be related to cardiovascular morbidity and mortality. Uric acid is a metabolic product synthesized from nucleic acids, amino acids and the Krebs cycle, reflecting a multiple metabolic associations in humans. The relation between uric acid and various cardiovascular metabolic parameters in Asians has rarely been reported on. In this study, we report the relationship between uric acid and various cardiovascular risk factors in 1,027 healthy Taiwanese adults living in Alien, an agricultural town in subtropical South Taiwan. Serum uric acid levels increased in proportion to age in women, but not in men. There were age and gender-specific correlations between uric acid and various cardiovascular metabolic parameters. Triglycerides and creatinine levels were two independent factors predicting serum uric acid levels in men, while only creatinine predicted uric acid levels in women of all age groups. Processes that influence the metabolism of uric acid and its association with other metabolic parameters differs by gender and age.

INTRODUCTION

The association between hyperuricemia and cardiovascular disease was previously controversial due to inconsistent data; however, the accumulation of recent data supports the association between uric acid and thrombotic events. Uric acid is associated with cardiovascular morbidity and mortality (Alderman, 2002). Hyperuricemia is associated with carotid atherosclerosis (Crouse *et al*, 1987; Nieto *et al*, 2000). Serum uric acid levels are a strong independent predictor for coronary heart disease (Longo-Mbenza *et al*, 1999; Wannamethee, 1999), total mortality in non-diabetic subjects (Tomita *et al*, 2000), stroke in non-insulin-dependent diabetics (Lehto *et al*, 1998), poor outcomes and further vascular events in all stroke patients (Weir *et al*, 2003), and also higher mortality in hemodialysis patients (Hsu *et al*, 2004).

Uric acid (monoanion urate at physiological pH value) was previously considered an inert metabolic end product of purine metabolism without physiological significance. Uric acid can enhance thrombogenesis, such as platelet hyperaggregation (Bourgain *et al*, 1982). Uric acid metabolism is influenced by a variety of metabolic disorders, such as in diabetes mellitus (Shinoda and Ishihara, 1990) and hyperlipidemia (Fox *et al*, 1985), and clinical conditions such as renal function, and life style, such as diet and environment, and gender and ethnicity. Serum uric acid levels reflect an association between thrombogenesis and metabolism *in vivo*. We present here the association between the subtropical Asian diet and lifestyle, which are different from the West and tropical countries, and serum uric acid levels and other metabolic parameters.

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MATERIALS AND METHODS

In Taiwan, the Central Health Insurance Bureau has provided a free-of-charge health examination to citizens over 40 years since 1996. In this study, we collected the health examination database for 1,769 adults living in Alien County, South Taiwan, from April to June 2000 at the Chang Yau Community Hospital, the only

local hospital in this agricultural town with 20,000 residents. The exclusion criteria included: 1. a history of hypertension, a systolic pressure >140 mmHg, a diastolic pressure >90 mmHg or on antihypertensive treatment currently; 2. a history of diabetes mellitus, a fasting blood glucose ≥150 mg/dl on two occasions with an increased glycosylated hemoglobin over 6.5% or on antidiabetic treatment currently; 3. a serum creatinine ≥1.5 mg/dl or a urine protein over 50 mg/dl; 4. serum alanine or glutamic aminotransferase ≥45 IU/l or a history of liver cirrhosis; 5. a history of cardiac disease, stroke, myocardial infarct or angina.

After an overnight fast, antecubital venous blood was drawn and mixed with 0.9% sodium citrate. The anticoagulated whole blood was checked for erythrocyte count, leukocyte count, platelet count and hemoglobin by a hematology autoanalyzer. Serum was examined for glucose, uric acid, total cholesterol (TC), triglyceride (TG), total protein, albumin, globulin, and urea nitrogen by the Beckman ASTRA system. These were completed within one hour of blood collection. The body mass index (BMI) was measured as weight (kg)/height $(m)^2$. The arterial blood pressure was measured by a mercury sphygmomanometer in a sitting position by the standard method. The mean arterial blood pressure (MABP) was calculated as (systole + 2 x diastole)/3.

The statistical analyses were performed by the one-way ANOVA least square difference, unpaired Student's *t*-test and simple correlation test. A probability of <0.05 was accepted as statistically significant.

RESULTS

After exclusion of 742 subjects, a total of 570 men and 457 women were enrolled in this study. The serum uric acid levels were significantly higher in men (6.893 ± 1.926 mg/dl) than in women (5.610 ± 1.703 mg/dl) (t=10.631, p<0.001). The leukocyte counts (t=5.156, p<0.001), erythrocyte counts (t=11.711, p<0.001), hemoglobins (t=17.129, p<0.001), albumins (t=2.551, p=0.011) and creatinine levels (t=11.761, p<0.001) were higher in the men, but the BMIs (t=-2.284, p=0.023), platelet counts (t=-3.360, p=0.001) and TCs (t=-3.351, p=0.001) were higher in the women (Table 1). The MABPs, pulse rates, globulins, FBG and TG levels did not differ between them. The simple

Table 1
The gender differences in the cardiovascular risk factors for 1,027 subjects.

Parameters	Men (n=570)	Women (n=457)	*t*-test for equality of means (2-tailed)	
			t-test	p-value
Body mass index (kg/m^2)	24.0529 ± 3.7497	24.6259 ± 3.8115	-2.284	0.023
MABP (mmHg)	89.9457 ± 9.6291	89.2534 ± 9.6965	1.080	0.281
Pulse rate (beats/minute)	75.40 ± 10.83	75.53 ± 10.03	-0.194	0.846
Leukocyte count (cells/ml)	7,711.45 ± 2073.15	7,038.65 ± 1,853.25	5.156	0.000
Erythrocyte count (10^6 cells/ml)	4.8317 ± 0.6231	4.3907 ± 0.5058	11.711	0.000
Hemoglobin (g/dl)	14.085 ± 1.471	12.562 ± 1.193	17.129	0.000
Platelet count (10^3 cells/ml)	247.09 ± 61.59	261.16 ± 64.53	-3.360	0.001
Albumin (g/dl)	4.056 ± 0.397	3.989 ± 0.398	2.551	0.011
Globulin (g/dl)	2.972 ± 0.383	2.960 ± 0.405	0.486	0.627
Fasting glucose (mg/dl)	102.62 ± 15.51	100.74 ± 14.51	1.885	0.060
Total cholesterol (mg/dl)	195.38 ± 40.99	204.74 ± 43.14	-3.351	0.001
Triglyceride (mg/dl)	180.30 ± 121.12	175.39 ± 142.24	0.561	0.575
Urea nitrogen (mg/dl)	16.64 ± 12.22	14.95 ± 8.86	2.391	0.017
Creatinine (mg/dl)	0.971 ± 0.229	0.806 ± 0.192	11.761	0.000
Uric acid (mg/dl)	6.893 ± 1.926	5.610 ± 1.703	10.631	0.000

MABP: mean arterial blood pressure; The bold p-values are statistically significant.

correlation test showed that BMI, TC, TG and creatinine levels correlated with the serum uric acid levels in both genders. However, the leukocyte counts and hemoglobin levels correlated to serum uric acid level in the men only, while the MABPs and fasting glucose levels were correlated with the uric acid levels in the women (Table 2). These findings indicate a gender-specific difference in uric acid levels, as well as an association between uric acid levels and cardiovascular risk factors in adults.

We separated our subjects into three groups by age: under 45 years as Group I, 45-64 years as Group II, and 65 years or more as Group III. In men, the serum uric acid levels did not vary by age. Only urea nitrogen increased by increasing age. The leukocyte counts and platelet counts were higher in Group I. The BMIs,

Table 2
A simple correlation between serum uric acid levels and cardiovascular risk factors.

Parameters/coefficient R value	Men	Women
Body mass index (kg/m^2)	0.1371[a]	0.1308[a]
MABP (mmHg)	0.0846	0.1163[a]
Pulse rate (beats/minute)	0.0187	0.0504
Leukocyte count (cells/ml)	0.0983[a]	0.0671
Erythrocyte count (10^6 cells/ml)	0.0849	0.0829
Hemoglobin (g/dl)	0.1128	0.0356
Platelet count (10^3 cells/ml)	-0.0300	-0.0014
Albumin (g/dl)	0.0219	-0.0408
Globulin (g/dl)	0.0371	-0.0136
Fasting glucose (mg/dl)	-0.0035	0.1300[a]
Total cholesterol (mg/dl)	0.1586[a]	0.2073[a]
Triglyceride (mg/dl)	0.1793[a]	0.1748[a]
Urea nitrogen (mg/dl)	0.1354[a]	0.1516[a]
Creatinine (mg/dl)	0.2765[a]	0.2885[a]

MABP: mean arterial blood pressure; [a]denotes p-value < 0.05

Table 3
The data of cardiovascular risk factors stratified by age for men and women.

Parameters	Gender	Group I	Group II	Group III
BMI (kg/m^2)	Men	25.24 ± 3.72	24.72 ± 3.39	23.02 ± 3.45[bc]
	Women	25.15 ± 4.21	25.00 ± 3.80	24.30 ± 3.95
MABP (mmHg)	Men	88.73 ± 8.85	87.89 ± 10.94	91.65 ± 9.06[bc]
	Women	86.87 ± 8.34	88.14 ± 9.63	90.58 ± 10.58[bc]
Pulse rate (beats/minute)	Men	76.69 ± 11.47	75.55 ± 11.32	76.08 ± 10.82
	Women	76.62 ± 10.65	75.74 ± 9.20	75.21 ± 10.38
Leukocyte count	Men	8,328.68 ± 2,269.18	7,639.20 ± 2,108.54	7,472.11 ± 1,805.58[ab]
(cells/ml)	Women	7,213.70 ± 1,653.89	7,047.85 ± 1,792.39	6,855.62 ± 1,751.40
Erythrocyte count	Men	5.04 ± 0.52	4.97 ± 0.64	4.66 ± 0.60[bc]
(10^6 cells/ml)	Women	4.43 ± 0.37	4.44 ± 0.53	4.30 ± 0.49[bc]
Hemoglobin (g/dl)	Men	14.57 ± 1.26	14.26 ± 1.67	13.66 ± 1.53[bc]
	Women	12.61 ± 1.35	12.69 ± 1.10	12.41 ± 1.25[c]
Platelet count	Men	268.68 ± 64.33	243.50 ± 55.41	233.61 ± 56.29[ab]
(10^3 cells/ml)	Women	279.68 ± 49.54	254.53 ± 60.75	248.80 ± 65.59[ab]
Albumin (g/dl)	Men	4.20 ± 0.36	4.13 ± 0.37	4.01 ± 0.38[bc]
	Women	4.18 ± 0.34	4.06 ± 0.37	3.98 ± 0.40[abc]
Fasting glucose (mg/dl)	Men	102.39 ± 15.63	104.44 ± 16.55	103.00 ± 15.19
	Women	99.42 ± 13.04	102.21 ± 14.40	100.74 ± 14.33
Total cholesterol (mg/dl)	Men	196.06 ± 38.97	189.52 ± 35.05	199.38 ± 41.60[c]
	Women	198.92 ± 46.27	207.50 ± 44.30	210.01 ± 39.44[b]
Triglyceride (mg/dl)	Men	218.25 ± 156.27	193.30 ± 128.99	154.05 ± 74.60[bc]
	Women	162.75 ± 130.20	178.32 ± 172.79	185.23 ± 130.27
Urea nitrogen (mg/dl)	Men	12.527 ± 4.368	15.289 ± 5.563	18.848 ± 5.108[abc]
	Women	11.329 ± 4.220	14.533 ± 4.840	15.838 ± 7.406[ab]
Creatinine (mg/dl)	Men	0.927 ± 0.188	0.949 ± 0.199	0.982 ± 0.255[c]
	Women	0.747 ± 0.154	0.793 ± 0.197	0.829 ± 0.222[b]
Uric acid (mg/dl)	Men	6.937 ± 2.026	6.671 ± 1.712	6.785 ± 1.968
	Women	4.962 ± 1.793	5.506 ± 1.533	5.649 ± 1.822[ab]

BMI: body mass index; MABP: mean arterial blood pressure
Least square difference, Group I *vs* II: a; Group I *vs* III: b; Group II *vs* III: c if $p < 0.05$
Group I: age <45 years; Group II: age 45~64 years; Group III: age ≥65 years

Table 4
A simple correlation between serum uric acid levels and cardiovascular risk factors in 570 men.

Parameters/coefficients	Group I	Group II	Group III
Body mass index (kg/m^2)	0.2390[a]	0.1178	0.0667
MABP (mmHg)	0.1502	0.0853	0.0498
Pulse rate (beats/minute)	0.0588	-0.0012	-0.0006
Leukocyte count (cells/ml)	0.0100	0.1034	0.1571[a]
Erythrocyte count (10^6 cells/ml)	0.0831	0.1858	0.0404
Hemoglobin (g/dl)	0.0773	0.2314[a]	0.0781
Platelet count (10^3 cells/ml)	-0.1349	0.1044	-0.0256
Albumin (g/dl)	-0.0980	0.2394[a]	0.0027
Fasting glucose (mg/dl)	-0.0018	0.0987	-0.0402
Total cholesterol (mg/dl)	0.1913[a]	0.2856[a]	0.0998
Triglyceride (mg/dl)	0.1798[a]	0.2032[a]	0.1912[a]
Urea nitrogen (mg/dl)	0.2079[a]	0.1912	0.1562[a]
Creatinine (mg/dl)	0.2053[a]	0.2021[a]	0.3436[a]

MABP: mean arterial blood pressure; [a]denotes p-value <0.05; Group I: age <45 years; Group II: age 45~64 years; Group III: age ≥65 years

Table 5
A simple correlation between serum uric acid levels and cardiovascular risk factors in 457 women.

Parameters/coefficients	Group I	Group II	Group III
Body mass index (kg/m^2)	0.2255[a]	0.0641	0.0439
MABP (mmHg)	0.1717[a]	0.2857[a]	-0.1340
Pulse rate (beats/minute)	0.1022	0.0042	0.0100
Leukocyte count (cells/ml)	0.1878[a]	0.0921	-0.0770
Erythrocyte count (10^6 cells/ml)	0.0324	0.1660	0.1412
Hemoglobin (g/dl)	0.0507	0.0944	-0.0004
Platelet count (10^3 cells/ml)	-0.0722	0.1046	0.0636
Albumin (g/dl)	-0.0824	0.1659	-0.0900
Fasting glucose (mg/dl)	0.1458[a]	0.1048	0.1263
Total cholesterol (mg/dl)	0.3110[a]	0.1954[a]	0.0889
Triglyceride (mg/dl)	0.1863[a]	0.1626	0.1794[a]
Urea nitrogen (mg/dl)	0.0792	0.3194[a]	0.1619
Creatinine (mg/dl)	0.2449[a]	0.2874[a]	0.3605[a]

MABP: mean arterial blood pressure; [a]denotes p-value < 0.05; Group I: age <45 years; Group II: age 45~64 years; Group III: age ≥65 years

erythrocyte counts, hemoglobin, albumin and TG levels were lower, but the MABPs, TC and creatinine levels were higher in Group III (Table 3). In women, serum uric acid levels increased with increasing age. Albumin decreased significantly with increasing age. The platelet counts were higher in Group I. The erythrocyte counts and hemoglobin levels were lower, but the MABPs, TC, urea nitrogen and creatinine levels were higher in Group III (Table 3).The pulse rates and fasting glucose levels did not change in either gender according to age. These results clearly point out an age-specific change in serum uric acid levels in women but not in men, and age- and gender-specific changes in various cardiovascular metabolic parameters.

In men, the BMI, TC, TG and creatinine levels correlated inversely with serum uric acid levels in Group I; the hemoglobin, albumin, TC, TG and creatinine levels correlated inversely with serum uric acid levels in Group II; and the leukocyte counts, TG and creatinine levels correlated inversely with serum uric acid levels in Group III (Table 4). An age-specific association between serum uric acid levels and these risk factors was identified; except for TG and creatinine levels which correlated with serum uric acid levels in all the age groups in men. In women, the BMI, MABP, leukocyte counts, fasting glucose, TC, TG and creatinine levels correlate inversely with serum uric acid in Group I; The MABP, TC, urea nitrogen and creatinine levels correlated inversely with serum uric acid levels in Group II, and TG and creatinine levels correlated inversely with serum uric acid levels in Group III (Table 5). An age-specific association between serum uric acid levels and these risk factors was found, except creatinine, which correlated with serum uric acid levels in all the age groups in women. Taken together, creatinine is the only factor which predicted the serum uric acid levels regardless of gender or age. Gender and age-specific associations between serum uric acid levels and various risk factors were obvious.

DISCUSSION

Taiwan is located in a subtropical area of the Pacific Rim. It shares the similar diet of low

animal fat and protein and high carbohydrates and fiber, with other Asian countries. The annual temperature is similar. We think our data may be of benefit to neighbored countries.

In this study, we illustrate a gender and age-specific association between serum uric acid and various cardiovascular metabolic parameters in the Taiwanese population. Nevertheless, uncontrollable factors are still present in this study. For example, the life style can not be well quantified. Other uncontrollable factors included the time of blood collection and the presence of underlying disease. Serum uric acid levels have diurnal variation in gout patients (Solakov *et al*, 1987). In our series, we tried to exclude patients with medical conditions, including gout. There is no report mentioning the diurnal variation of serum uric acid levels in healthy individuals.

In our study, we had several findings: 1) serum uric acid levels were higher in men than in women within the same age groups; 2) serum uric acid levels increased with increasing age in women but not in men; and 3) serum uric acid levels were correlated with BMI, TC, TG, creatinine and urea nitrogen. Some of these findings are in agreement with previous reports. Serum uric acid levels were also higher in men than in women in caucasians (Tuttle *et al*, 2001). The effect of age on serum uric acid levels is controversial. In some studies, increasing serum uric acid levels are associated with increasing age (Kuzuya *et al*, 2002), but some studies do not support this finding. In our study, the finding of age-related changes in serum uric acid levels in women is not surprising, given the influence sex hormones have on uric acid regulation and purine biosynthesis (Adamopoulos *et al*, 1977; Marinello *et al*, 1985). A direct relationship between serum uric acid levels and BMI, TC and TG levels has been extensively reported on worldwide in caucasians (Di Sciascio *et al*, 1994; Church *et al*, 2002) and in Taiwanese (Chu *et al*, 2000). There is a metabolic association between uric acid and lipids.

Renal function correlated with serum uric acid levels in our series, regardless of gender and age. Uric acid is weakly bound to plasma proteins and is found in the free form in a ratio of about 50:50. The free form of uric acid is excreted from the distal tubules in the kidneys. A decline in renal function is associated with an increase in serum creatinine levels, and a decrease in uric acid excretion, therefore, hyperuricemia ensues. Deposition of urate crystals in the tubules may perturb renal function. Uric acid precipitates in an acidic or cationic environment. Uric acid precipitation may be enhanced by acidification of the blood from the high animal protein in diet found in caucasians. In Taiwan, a high concentration of calcium, magnesium and other trace elements is found in some water sources and this may enhance uric acid precipitation in the distal renal tubules.

A weak correlation is also noted between serum uric acid levels and urea nitrogen. In view of the direct correlation between serum uric acid levels and creatinine in our series, this finding may reflect renal function as well. Urea nitrogen is also a metabolic marker for protein metabolism, and may be linked to an excess of amino acids or proteins which come from the diet. A full investigation of protein sources and their metabolism in the Asian diet may elucidate this relationship.

Our study reveals a gender and age-specific correlation between uric acid and cardiovascular metabolic risk factors. Uric acid is a metabolic product related to a number of other metabolic processes. Our results suggest that certain factors may be age and gender specific.

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