Association Between Serum Uric Acid Level and Components of the Metabolic Syndrome

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Background: Serum uric acid (UA) level has been suggested to be associated with factors that contribute to the metabolic syndrome. However, the association between metabolic syndrome and UA has not been elucidated. We sought to determine the association between serum UA level and the number of components that contribute to the metabolic syndrome, and which component was associated most with higher serum UA level.

Methods: A consecutive sample was taken of the health examinations of all hospital staff who were assessed between January 2004 and December 2004 in a medical center. A total of 3,065 subjects aged 18 to 81 years (635 males, 2,430 females) participated. Blood tests and all physical variables were examined using standard methods. Subjects were divided into 5 groups according to their possession of 0, 1, 2, 3 or ≥4 components of the metabolic syndrome. The differences in all variables between groups were analyzed by ANOVA. The relationship between serum UA level and the number of metabolic components was determined by linear regression analysis. The contribution to elevated UA of possessing different risk factors was determined by a multivariate linear regression model.

Results: Mean serum UA level increased as the number of metabolic factors increased. Serum UA level was higher in subjects with abnormal triglyceride (TG), waist circumference, high-density lipoprotein cholesterol (HDL-C) level and blood pressure (BP), with mean increases in UA level of 22.8, 21.4, 14.4 and 9.4 μmol/L, respectively ($p \leq 0.001$), compared to subjects with normal levels. After controlling for body mass index, abnormal TG, HDL-C and BP continued to account, in order of influence, for elevated UA.

Conclusion: Serum UA level was elevated significantly as the number of metabolic components increased. Abnormal TG had the most influence on serum UA. A prospective study is warranted to determine if the prevention or treatment of hyperuricemia affects the development of metabolic syndrome. [*J Chin Med Assoc* 2006;69(11):512–516]

Key Words: cardiovascular disease, metabolic syndrome, uric acid

Introduction

Cardiovascular disease has been suggested to be associated with increased serum uric acid (UA) level[1–3] and an increased number of the components that contribute to metabolic syndrome.[4] There is also an established link between serum levels of UA and individual risk factors such as hypertension[5] or dyslipidemia[6,7] that increase cardiovascular risk. However, the association between an increasing number of metabolic components and serum UA has not been well studied except for 2 previous studies in the West.[4,8] We sought to determine the association between serum UA and the number of risk factors that contribute to the metabolic syndrome, and which factor is associated most with higher serum UA level in a cohort of hospital staff in a medical center in Taiwan.

Methods

This was a cross-sectional study of a consecutive sample of 3,065 staff who underwent health examination between January 2004 and December 2004 at a medical center in Taiwan. Blood tests and all physical variables were examined at nearly the same time. Blood

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pressure (BP) was measured using an automated sphygmomanometer, with the patient in the sitting position before the blood test. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Waist circumference (WC) was measured with the measuring tape positioned midway between the lowest rib and the superior border of the iliac crest while the patient exhaled normally.[9]

The blood sample was collected in the morning after an 8–12-hour fast. Levels of glucose, UA, creatinine, liver enzymes, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) were determined in the hospital laboratory using standard methods. The components that contribute to metabolic syndrome were defined as high BP (≥130/85 mmHg), truncal obesity (WC > 90 cm for men, > 80 cm for women), hypertriglyceridemia (> 150 mg/dL or 1.7 mmol/L), low HDL-C (< 40 mg/dL or 1.0 mmol/L for men, < 50 mg/dL or 1.3 mmol/L for women) and hyperglycemia (fasting blood glucose level ≥110 mg/dL or 6.1 mmol/L).[10] Subjects were divided into 5 groups according to their possession of 0, 1, 2, 3 or ≥4 components of the metabolic syndrome.

Baseline demographic data in the 5 groups were descriptively summarized. Continuous variables were expressed as mean ± standard deviation. Categorical variables were presented as percentages. The differences in all variables between groups were compared using ANOVA. The relationship between serum UA and increasing number of risk factors was determined by linear regression analysis. The contribution to elevated serum UA of possessing different risk factors was determined by a multivariate linear regression model. Significance was defined as $p < 0.05$ for all statistical tests, which were performed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA) for Windows.

Results

The demographic data of the study cohort are presented in Table 1. All variables showed significant differences between groups, with an increasing trend as the number of components increased (except for HDL-C, which showed a decreasing trend). Mean serum UA levels increased in subjects who had 0, 1, 2, 3 and ≥4 components and demonstrated a significant linear trend. By linear regression analysis and adjusting

Table 1. Demographic data of the population based on the number of risk factors*

	Number of metabolic risk factors				
	0 (*n* = 1,555)	1 (*n* = 878)	2 (*n* = 411)	3 (*n* = 158)	≥4 (*n* = 63)
Variable					
Sex (% males)	10.9	25.1	37.0	41.1	44.4
Age (yr)	30.7 ± 7.5	33.8 ± 9.2	36.6 ± 10.2	38.2 ± 10.0	37.7 ± 9.7
BMI (kg/m^2)	20.68 ± 2.33	22.69 ± 3.15	25.81 ± 3.62	27.22 ± 3.78	28.91 ± 3.74
WC (cm)	70.80 ± 6.38	77.36 ± 8.75	85.63 ± 8.17	89.57 ± 9.82	93.57 ± 8.94
SBP (mmHg)	108.5 ± 9.2	119.8 ± 13.6	126.2 ± 15.9	129.5 ± 16.5	131.2 ± 15.6
DBP (mmHg)	73.7 ± 6.5	82.1 ± 9.9	86.7 ± 10.1	90.0 ± 11.4	92.4 ± 10.4
FPG (mmol/L)	4.75 ± 0.38	4.92 ± 0.51	5.19 ± 1.12	5.51 ± 1.32	6.29 ± 1.79
UA (μmol/L)	293 ± 68	326 ± 85	362 ± 97	292 ± 100	419 ± 104
Cr (μmol/L)	73 ± 12	77 ± 15	80 ± 18	82 ± 18	82 ± 16
HDL-C (mmol/L)	1.76 ± 0.31	1.58 ± 0.35	1.38 ± 0.34	1.19 ± 0.23	1.04 ± 0.15
TG (mmol/L)	0.70 ± 0.28	0.91 ± 0.44	1.44 ± 0.98	2.12 ± 1.30	2.66 ± 1.09
LDL-C (mmol/L)	2.60 ± 0.65	2.84 ± 0.80	3.19 ± 0.82	3.35 ± 0.77	3.43 ± 0.83
TC (mmol/L)	4.74 ± 0.76	4.86 ± 0.94	5.19 ± 1.00	5.36 ± 0.88	5.44 ± 1.02
AST (IU/dL)	19.8 ± 11.3	20.7 ± 9.5	24.2 ± 14.7	26.5 ± 20.4	33.3 ± 24.9
ALT (IU/dL)	16.7 ± 20.0	20.3 ± 21.0	28.9 ± 28.0	36.2 ± 37.2	50.2 ± 42.1
WBC (×10^9/L)	5.8 ± 1.5	6.1 ± 1.6	6.6 ± 1.7	6.6 ± 1.6	7.1 ± 1.7
RBC (×10^{12}/L)	4.43 ± 0.42	4.59 ± 0.50	4.76 ± 0.51	4.84 ± 0.49	4.87 ± 0.45
Platelets (×10^9/L)	255.4 ± 54.5	265.8 ± 60.5	272.8 ± 59.4	287.7 ± 57.9	293.4 ± 64.0

**All variables showed significant differences between groups ($p < 0.05$). BMI = body mass index; WC = waist circumference; SBP = systolic blood pressure; DBP = diastolic blood pressure; FPG = fasting plasma glucose; UA = uric acid; Cr = creatinine; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; AST = aspartate aminotransferase; ALT = alanine aminotransferase; WBC = white blood cell count; RBC = red blood cell count.*

Table 2. Mean increased level of uric acid, comparing abnormal to normal metabolic components after adjusting for confounding variables* with and without body mass index (BMI)

Metabolic factor	All factors except BMI adjusted for		All factors adjusted for	
	Mean (95% CI)	*p*	Mean (95% CI)	*p*
Constant	93.3 (56.8–129.8)	< 0.001	22.4 (–16.4–61.1)	0.258
AbnTG	22.8 (14.2–31.5)	< 0.001	19.8 (11.3–28.4)	0.07
AbnHDL-C	14.4 (6.6–14.1)	< 0.001	12.0 (4.3–19.6)	0.002
AbnBP	9.4 (4.0–14.8)	0.001	6.6 (1.2–11.9)	0.016
AbnWC	21.4 (15.3–27.5)	< 0.001	2.8 (–4.4–9.9)	0.445
AbnFPG	–7.1 (–19.8–5.5)	0.268	–9.2 (–21.7–3.2)	0.146
R^2	0.457		0.473	

**Confounding variables were sex, age, body mass index, total cholesterol, low-density lipoprotein cholesterol, creatinine, aspartate aminotransferase, alanine aminotransferase, white blood cell count, red blood cell count, and platelet number. AbnTG = triglycerides > 150 mg/dL or 1.7 mmol/L; AbnHDL-C = high-density lipoprotein cholesterol < 40 mg/dL or 1.0 mmol/L for men and < 50 mg/dL or 1.3 mmol/L for women; AbnBP = systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg; AbnWC = waist circumference > 90 cm for men and > 80 cm for women; AbnFPG = fasting plasma glucose ≥ 110 mg/dL or 6.1 mmol/L.*

for other confounding factors (age, BMI, serum creatinine, LDL-C, TC, aspartate aminotransferase, alanine aminotransferase, white blood cell count, red blood cell count, platelet number), it was found that men had a higher serum UA level than women with the same risk factors, and there were significant differences in UA levels between groups as the number of risk factors increased ($p < 0.001$).

Table 2 lists the mean increased level of UA in subjects with various components of the metabolic syndrome after adjusting for confounding variables with and without BMI. Serum UA level was highest in subjects with abnormal levels of TG, with a mean increase in UA level of 22.8 μmol/L compared to subjects with normal TG. People who had abnormal WC, HDL-C and BP showed increases in UA levels of 21.4, 14.4 and 9.4 μmol/L, respectively. Having an abnormal level of fasting glucose did not affect serum UA level. After controlling for BMI, which may be a confounding factor for UA level and is well correlated to WC, the apparent influence of abnormal metabolic components on UA decreased. Abnormal TG had the greatest effect on UA level, while abnormal HDL-C and BP, in order of influence, were also associated with elevated UA.

Discussion

This study showed the significant relationships between serum UA and 5 components of the metabolic syndrome. As the population with 5 components was small in our study, this group was combined with people who had 4 components. We found that serum UA level was significantly higher and increased in a linear fashion in subjects who had an increased number of risk factors; this relationship remained significant even after controlling for other confounding factors. This result has also been demonstrated in other studies.[4–8] We further separated subjects into male and female groups, and found that serum UA level was higher in men. This result was not unexpected as it is known that estrogen promotes excretion of UA,[11,12] and the mean age of the female cohort was 32.1 years (range, 30.5–38.6).

Elevated serum UA levels are commonly seen in association with individual cardiovascular risk factors such as hypertriglyceridemia,[6,13,14] hypertension,[5] obesity,[6,15] and hyperglycemia,[16–18] a cluster that, when found together in the same person, characterizes the so-called metabolic syndrome. In our study, abnormal TG had a stronger association with increasing serum UA level than all the other components. This finding is in agreement with other studies,[6,13,14] which have consistently found that TG correlates independently with UA level. The mechanism for the strong association between TG and UA concentrations has not been elucidated. Although genetic factors are associated with the concurrence of gout and hypertriglyceridemia,[19,20] investigators have generally concluded that hyperuricemia and hypertriglyceridemia reflect the lifestyle of the patient more than genetic factors because obesity is also associated with these characteristics.[21] Abnormal HDL-C was also associated with elevated UA in our study. This is reasonable because serum UA level correlated negatively with HDL-C in other studies.[22,23] Hyperinsulinemia has been shown to increase tubular resorption of sodium, with a consequent impairment in the kidney's ability to excrete UA.[17] So, people with normal glycemia may have

higher UA level if they are more insulin resistant. On the other hand, hyperglycemia (>144 mg/dL) with glucosuria may increase UA excretion,[16,18] resulting in lower serum UA. Since the cut-off point of abnormal fasting glucose in metabolic syndrome is 110 mg/dL, not representing hyperinsulinemia, it is not surprising that there was no significant difference in serum UA level between the normal and abnormal fasting glucose groups. Insulin resistance is also associated with higher TG,[24] WC,[25,26] and lower HDL-C.[24] Therefore, it can be proposed that the elevated UA level in our subjects who had abnormal TG, WC and HDL-C was due to concomitant higher insulin resistance. The association of higher serum UA level with higher BP has been reported in other studies.[5,27] It was also found in our study that subjects with abnormal BP had higher UA levels. UA may contribute to endothelial dysfunction and may play a causal role in the pathogenesis of hypertension.[27] We conclude that higher BP was associated with higher UA level in our study, although whether or not high BP accounted for hyperuricemia is not clear.

It has been suggested that UA may be a cause of the metabolic syndrome.[28] In fructose-fed rats, lowering UA level prevented or improved most features of the metabolic syndrome, including the prevention of hyperinsulinemia, hypertriglyceridemia, hypertension and weight gain.[28] Studies in humans have found that UA is a potent predictor of hyperinsulinemia[29] and weight gain.[30] This is possibly due to its ability to inhibit endothelial function by impairing nitric oxide production.[27,28] Whether UA is a bystander, a partner or an initiator of the metabolic syndrome cannot be answered from the results of this cross-sectional study; a prospective study is needed to clarify their interrelationships.

This study had several limitations. First, the data analysis was restricted due to the cross-sectional design of the study. To confirm an interdependence of changes in the risk factor components of metabolic syndrome and serum UA level, a prospective study is needed. Second, other confounding factors affecting UA, such as alcohol consumption, the use of diuretics, physical activity, and a diet habitually high in purines, were not considered in this study. Since alcohol consumption is significantly associated with elevated UA,[31] there may be some statistical bias due to misclassification. Finally, the cohort was restricted to staff in a medical center, so the results in this study may not be applicable to the general population of Taiwan.

From our study, serum UA level increased as the number of components of the metabolic syndrome increased. Subjects with abnormal TG, WC, HDL-C and BP had higher UA, in decreasing order of influence, compared to subjects with normal levels. Elevated UA was not noted in the abnormal fasting blood glucose group compared to the group with normal levels. Although UA had a strong association with metabolic syndrome, a prospective study is warranted to determine if the prevention or treatment of hyperuricemia affects the development of metabolic syndrome.

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