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Relationship Between Serum Uric Acid Concentration and Insulin Resistance and Metabolic Syndrome

Tae Woo Yoo, MD; Ki Chul Sung, MD; Hun Sub Shin, MD; Byung Jin Kim, MD; Bum Soo Kim, MD; Jin Ho Kang, MD; Man Ho Lee, MD; Jung Ro Park, MD; Hyang Kim, MD; Eun Jung Rhee, MD; Won Young Lee, MD; Sun Woo Kim, MD; Seung Ho Ryu, MD*; Dong Geuk Keum, MD**

Background Associations between hyperuricemia, cardiovascular diseases and diabetes have been reported, but few of the studies have been conducted in the Korean population. The present study examined a Korean adult population with respect to the relationships between serum uric acid concentrations and hypertension, insulin resistance, and the risk factors of metabolic syndrome.

Methods and Results A total of 53,477 subjects were divided into 4 groups according to serum uric acid quartiles. The incidence of hypertension in all subjects was higher in the first quartile than in the third plus fourth quartile (odds ratio (OR) 1.192, $p<0.001$). Homeostasis model assessment index was found to be associated with serum uric acid concentration in all subjects (OR 1.193, $p<0.001$), and the serum uric acid concentration was positively correlated with the risk factors of metabolic syndrome. In addition, the number of metabolic syndrome variables increased as serum uric acid concentration increased.

Conclusions Serum uric acid concentration was found to be independently correlated with hypertension, insulin resistance and the risk factors of metabolic syndrome. In addition, even those with a serum uric acid concentration in the normal range showed an increased risk of metabolic syndrome as serum uric acid concentration increased. (*Circ J* 2005; **69:** 928–933)

Key Words: Hypertension; Insulin resistance; Metabolic syndrome; Uric acid

Metabolic syndrome is a cluster of metabolic abnormalities related to an increased risk of cardiovascular disease[1] and recent research has demonstrated that adipocytokines, especially adiponectin, are associated with metabolic syndrome[2] In terms of the evaluation and management of hypercholesterolemia (a risk factor of cardiovascular disease and a causative factor of death in more than 40% of heart-related deaths) according to the recommendations of the 2001 Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) Ⅲ Guidelines, the risk factors for the development of metabolic syndrome are visceral obesity, hypertension, hypertriglyceridemia, a low level of high-density lipoprotein cholesterolemia, and an impaired glucose tolerance[3]

Hyperuricemia is also considered by some investigators to be a component of metabolic syndrome that reflects insulin resistance[4,5] In several epidemiological studies, a close relationship between hyperuricemia and hypertension, heart failure and other cardiovascular diseases has been reported[6–9] and correlations between hyperuricemia and obesity, dyslipidemia, and diabetes have also been recently reported[10–12] However, studies of Asians, who differ physically from Caucasians, are relatively rare. In Korea, knowledge of the general adult population without type 2 diabetes, hypertension and other diseases is inadequate, and no study has been performed on the association between the newly defined metabolic syndrome and hyperuricemia in the Korean population. Hence, this study investigated Korean adults who had undergone health screening to assess the correlation between increased serum uric acid concentration and hypertension, insulin resistance, and other risk factors of metabolic syndrome.

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*Departments of Internal Medicine, *Occupational Medicine and **Laboratory Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea*

Mailing address: Ki Chul Sung, MD, Department of Internal Medicine, Kangbuk Samsung Hospital, Pyung Dong, Jongro-Ku, Seoul 110-746, Korea. E-mail: kcmd.sung@samsung.com

Methods

Study Population

The study group comprised 53,477 individuals (34,169 males, 19,308 females), who underwent health screening at Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea between January 1, 2002, and December 31, 2002. Subjects who were taking diuretics, antihypertensive or antidiabetic agents, lipid-lowering agents, hyper- or hypouricemic agents, and those with any clinical suspicion of malignancy, acute infectious disease, acute inflammatory disease or renal disease were excluded.

Physical Examination and Blood Pressure (BP)

Height, weight, waist–hip circumference and systolic and diastolic BP were measured. According to the Hypertension Detection and Follow-up Program protocol[13] BP was measured using a sphygmomanometer after the subjects had rested for more than 5 min. For those with a systolic BP >140 mmHg and a diastolic BP >90 mmHg (defined as hypertension by the 2003 JNC-7[14]) BP was measured on a further 2 occasions after resting, and average

Table 1 Characteristics of the Study Population (n=53,477)

	Male (n=34,169)		Female (n=19,308)		Total	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	40.3	8.5	41.4	10.2	40.7	9.1
Systolic blood pressure (mmHg)	117.4	14.2	113.3	17.7	116.0	15.6
Diastolic blood pressure (mmHg)	76.7	10.7	71.8	11.2	75.0	11.1
Body mass index (kg/m^2)	24.2	2.8	22.5	3.0	23.6	3.0
Heart rate (beats/min)	66.0	9.3	68.2	9.4	66.8	9.4
Fasting serum glucose (mg/dl)	94.1	19.1	89.4	16.9	92.4	18.5
Total cholesterol (mg/dl)	206.1	35.6	198.3	36.1	203.3	36.0
LDL-C (mg/dl)	121.2	29.9	113.7	29.9	118.5	30.1
HDL-C (mg/dl)	52.4	12.0	61.7	14.6	55.7	13.8
Triglycerides (mg/dl)	160.2	106.1	113.0	77.7	143.1	99.4
Apolipoprotein A1 (mg/dl)	117.7	21.3	120.9	22.5	119.0	21.9
Apolipoprotein B (mg/dl)	103.8	25.9	93.9	26.7	99.6	26.7
Uric acid (mg/dl)	6.0	1.20	4.1	0.86	5.3	1.42
Insulin (fasting) (μIU/ml)	7.9	3.09	7.6	2.80	7.8	2.99
HOMA index*	1.8	0.88	1.7	0.77	1.8	0.84
Waist (cm)	83.7	7.21	73.2	8.0	79.9	9.1
Waist/hip ratio	0.88	0.05	0.77	0.06	0.84	0.07
Hypertension (%)	20.6		13.6		18.2	
DM (%)	4.2		2.6		3.6	

See text for calculation of HOMA index. LDL-C, serum low-density lipoprotein cholesterol; HDL-C, serum high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; DM, diabetes mellitus.

values were then taken. Height and weight were measured using an automatic scale, and body mass index (BMI) was calculated from that data (kg/m^2). The measurement around the umbilical area while standing straight was used as the waist circumference and the measurement around the greater trochanter of the femur as the hip circumference. Homeostatic model assessment (HOMA) indices were used as markers of insulin resistance and calculated as follows:[15]

HOMA index = [fasting insulin (μIU/ml) × fasting serum glucose (mmol/L)]/22.5.

Blood Sampling

After a 12-h fast, a venous blood sample was obtained from each subject for measurement of serum uric acid, fasting blood glucose, total cholesterol, serum triglyceride, and high- and low-density lipoprotein cholesterol concentrations using an automatic analyzer (Advia 1650, Bayer, Germany). The serum uric acid concentrations were measured using the Uricase EMST method, and fasting blood glucose was measured by the hexokinase method (Hitachi 747 automatic analyzer, Hitachi, Japan). The fasting insulin concentration was measured using an immunoradiometric assay (Biosource, Belgium; intra- and inter-assay coefficient of variability 2.1–4.5% and 4.7–12.2%, respectively). Total cholesterol and serum triglyceride were measured using enzymatic colorimetric tests. High-density lipoprotein cholesterol was measured by the selective inhibition method and low-density lipoprotein cholesterol by homogenous enzymatic colorimetric test. Apolioprotein B (Apo B) and apolipoprotein AI concentrations were determined using the rate nephelometry method (Beckman) and high-sensitivity C-reactive protein (hsCRP) was determined by immunonephelometry (Behring Nephelometer II, Dade Behring Marburg GmbH, Germany); any concentration of hsCRP ≤0.2 mg/L was considered to be 0.1 mg/L.

Definition of Metabolic Syndrome

In the recently reported 2001 NCEP-ATP III diagnosis standard,[3] visceral obesity in subjects from the Asian-Pacific region is defined by substituting their standard waist circumferences;[16] that is, a subject was defined to have metabolic syndrome in the present study when 3 of any of the 5 following items were present: (1) visceral obesity (for males, a waist circumference ≥90 cm, for females, ≥80 cm); (2) hypertriglyceridemia (≥150 mg/dl); (3) a low level of high-density lipoprotein cholesterolemia [for males: <40 mg/dl, for females: <50 mg/dl]; (4) BP ≥130/85 mmHg; and (5) fasting blood glucose ≥110 mg/dl. In addition, subjects with a fasting glucose concentration ≥126 mg/dl and those receiving diabetic drugs were considered to have diabetes.

Statistical Analysis

Statistical analysis was performed using Windows SPSS program (ver. 8.0 or 10.0; Chicago, IL, USA). Statistical results are presented as means ± standard error or as 95% confidence intervals (CI). To analyze the correlations between serum uric acid concentration and hypertension, insulin resistance, or the risk factors of metabolic syndrome, the study population was divided into quartiles based on serum uric acid concentrations. The various group values were compared by one-way ANOVA, and odds ratios (OR) were determined by ANOVA testing and χ^2 testing. Relative risks were analyzed by using multiple logistic regression analysis and p-values of <0.05 were considered statistically significant.

Results

Correlation Between Serum Uric Acid Concentration and the Clinical Characteristics of the Study Population

The male to female ratio of the study subjects was 1.77:1 and the average age was 40.7 years (±9.1). Based on fasting serum uric acid concentrations, the subjects were divided into 4 groups: quartile 1, <4.2 mg/dl (n=12,338); quartile 2, 4.2–5.29 mg/dl (n=13,564); quartile 3, 5.3–6.29 mg/dl (n=13,540); and quartile 4, >6.29 mg/dl (n=13,943).

Were hypertensive, The incidence of hypertension was 18.2% (9,462 subjects: 7,034 males (20.6%); 2,428 females

Table 2 Prevalence of Hypertension by Uric Acid Concentration

Uric acid quartile	Elevated systolic hypertension		Elevated diastolic hypertension		Hypertension	
	Prevalence (%)*	95% CI	Prevalence (%)*	95% CI	Prevalence (%)*	95% CI
I (<4.2)	8.7	(8.2–9.2)	9.6	(9.1–10.2)	12.2	(11.7–12.9)
II (4.2–5.29)	10.4	(9.9–11.0)	13.7	(13.2–14.3)	16.4	(15.7–17.0)
III (5.3–6.29)	10.7	(10.2–11.2)	17.2	(16.6–17.9)	19.5	(18.8–20.2)
IV (>6.29)	12.2	(11.6–12.7)	21.7	(21.0–22.4)	23.6	(22.9–24.4)

χ^2 for linear trend; *p<0.001. CI, confidence interval.

Table 3 Univariate Correlation, Age, Blood Pressure, Metabolic and Anthropometric Variables

	Uric acid	SBP	DBP	Insulin	HOMA	BMI	Waist	Hip	WHR
Age	–0.067†	0.336†	0.252†	–0.009*	0.67†	0.143†	0.229†	0.023†	0.292†
Uric acid		0.142†	0.208†	0.159†	0.157†	0.354†	0.490†	0.177†	0.521†
SBP			0.828†	0.158†	0.208†	0.297†	0.299†	0.203†	0.261†
DBP				0.157†	0.202†	0.315†	0.314†	0.216†	0.270†
Insulin					0.894†	0.420†	0.353†	0.355†	0.231†
HOMA						0.430†	0.391†	0.323†	0.303†
BMI							0.827†	0.803†	0.560†
Waist								0.671†	0.898†
Hip									0.225†
WHR									

	Uric acid	FBG	TG	HDL-C	LDL-C	hsCRP	BMI	Waist	SBP	DBP
Uric acid	1.000†	0.060†	0.283†	–0.285†	0.167†	0.101†	0.354†	0.490†	0.142†	0.208†
FBG		1.000†	0.247†	–0.130†	0.086†	0.120†	0.200†	0.248†	0.197†	0.179†
TG			1.000†	–0.343†	0.018†	0.053†	0.334†	0.362†	0.194†	0.208†
HDL-C				1.000†	–0.010†	–0.107†	–0.320†	–0.412†	–0.071†	–0.093†
LDL-C					1.000†	0.028†	0.252†	0.245†	0.123†	0.122†
hsCRP						1.000†	0.149†	0.161†	0.091†	0.076†
BMI							1.000†	0.827†	0.297†	0.315†
Waist								1.000†	0.299†	0.314†
SBP									1.000†	0.828†
DBP										1.000†

*SBP, systolic blood pressure (mmHg); DBP, diastolic blood pressure (mmHg); Insulin, fasting serum insulin (pmol/L); HOMA, homeostasis model assessment; BMI, body mass index (kg/m^2); WHR, waist to hip ratio; FBG, fasting serum glucose (mg/dl); TG, serum triglyceride (mg/dl); hsCRP, high sensitivity C-reactive prptein; HDL-C, serum high-density lipoprotein cholesterol (mg/dl); LDL-C, serum low-density lipoprotein cholesterol (mg/dl). *p<0.05, †p<0.01.*

(13.6%)), and their mean systolic and diastolic BPs were 116.0±15.6 mmHg and 75.0±11.1 mmHg, respectively.

Mean fasting serum glucose, serum triglyceride, serum high-density lipoprotein cholesterol, serum low-density lipoprotein cholesterol, Apo B, and apolipoprotein AI concentrations were 92.4±18.5 mg/dl, 143.1±99.4 mg/dl, 55.7±13.8 mg/dl, 118.5±30.1 mg/dl, 99.6±26.7 mg/dl and 119.0±21.9 mg/dl, respectively. Mean BMI, waist/hip circumference ratio, and HOMA index for all subjects were 23.6±3.0 kg/m^2, 0.84±0.07 cm and 1.8±0.84, respectively (Table 1).

Serum Uric Acid Concentration and the Incidence of Hypertension

The serum uric acid concentration quartiles were compared and a comparison of the lowest and highest groups revealed that as serum uric acid concentration increased, the incidence for hypertension also increased (Table 2).

Correlations Between Serum Uric Acid Concentration, and Hypertension, Insulin Resistance and the Risk Factors of Metabolic Syndrome

In terms of the correlations between serum uric acid concentration and hypertension, insulin resistance and the risk factors of metabolic syndrome by univariate analysis, the factors that were positively correlated weresystolic and diastolic BP, fasting serum insulin concentration, HOMA, BMI, waist-hip ratio, fasting serum glucose concentration, and hsCRP concentration. In addition, an inverse correlation was found between age and the serum concentration of high-density lipoprotein cholesterol (Table 3).

Correlation Between Serum Uric Acid Concentration and Hypertension

Multiple regression analysis showed that when systolic and diastolic BP were independent variables, as BP increased, the serum uric acid concentration also increased (Table 4). When multiple regression analysis of systolic and diastolic BP and serum uric acid concentration was performed after adjusting for gender, age, HOMA, BMI, and waist circumference to analyze the incidence of hypertension according to the increase of serum uric acid concentration, we found that as the HOMA, BMI, and waist circumference in man increased, the incidence of hypertension increased. With regard to serum uric acid concentration, vs the first quartile, the OR of the second quartile was 1.128 (95% CI 0.998–1.276), and the incidence of hypertension tended to increase in those with a high serum uric

Table 4 Stepwise Multivariate Regression Analyses With Systolic and Diastolic Blood Pressure as Dependent Variables

	Standardized coefficients (B)	*t*	*p-value*
Model 1: Dependent variables: SBP (mmHg)			
Age	*0.292*	*47.013*	*<0.001*
Waist	*0.120*	*8.192*	*<0.001*
BMI	*0.110*	*9.098*	*<0.001*
HOMA	*0.083*	*12.495*	*<0.001*
Sex	*–0.056*	*–5.996*	*<0.001*
Uric acid	*0.047*	*5.842*	*<0.001*
Model 2: Dependent variables: DBP (mmHg)			
Age	*0.223*	*35.065*	*<0.001*
Waist	*0.151*	*10.101*	*<0.001*
BMI	*0.100*	*8.099*	*<0.001*
HOMA	*0.076*	*11.242*	*<0.001*
Sex	*–0.062*	*–6.437*	*<0.001*
Uric acid	*0.050*	*6.129*	*<0.001*

SBP, systolic blood pressure; BMI, body mass index; HOMA, homeostasis model assessment; DBP, diastolic blood pressure.

Table 5 Multivariate Logistic Regression Analyses With Hypertension as an Dependent Variable

Variable	*Odds*	*95% CI*	*p-value*
Sex	*0.715*	*(0.630–0.812)*	*<0.001*
Age	*1.074*	*(1.070–1.079)*	*<0.001*
HOMA	*1.193*	*(1.144–1.244)*	*<0.001*
BMI	*1.101*	*(1.075–1.129)*	*<0.001*
Waist	*1.032*	*(1.022–1.042)*	*<0.001*
Uric acid quartile			
I	*1*		
II	*1.128*	*(0.998–1.276)*	*0.054*
III	*1.192*	*(1.038–1.368)*	*0.013*
IV	*1.408*	*(1.221–1.623)*	*<0.001*

CI, confidence interval; HOMA, homeostasis model assessment; BMI, body mass index.

Table 6 Analysis of Covariance: Age-Adjusted Blood Pressure and Metabolic Variables vs Serum Uric Acid Concentration

	Uric acid (mean±SD)				*p-value*
	I (<4.2)	*II (4.2–5.29)*	*III (5.3–6.29)*	*IV (>6.29)*	
SBP (mmHg)	*112.7 (±16.3)*	*115.3 (±16.3)*	*116.9 (±14.7)*	*118.6 (±14.6)*	*<0.001*
DBP (mmHg)	*71.6 (±10.8)*	*73.9 (±11.0)*	*76.0 (±10.7)*	*77.8 (±11.0)*	*<0.001*
Heart rate (beats/min)	*67.7 (±9.4)*	*67.0 (±9.4)*	*66.0 (±9.4)*	*66.6 (±9.4)*	*<0.001*
FBG (mg/dl)	*90.6 (±21.9)*	*92.4 (±20.4)*	*92.8 (±16.8)*	*93.6 (±14.1)*	*<0.001*
TC (mg/dl)	*194.7 (±34.7)*	*200.1 (±35.4)*	*204.9 (±35.1)*	*212.4 (±36.3)*	*<0.001*
LDL-C (mg/dl)	*111.2 (±28.4)*	*116.4 (±29.7)*	*120.7 (±29.6)*	*124.7 (±30.9)*	*<0.001*
HDL-C (mg/dl)	*61.7 (±14.7)*	*57.5 (±14.1)*	*53.2 (±12.4)*	*51.2 (±11.5)*	*<0.001*
TG (mg/dl)	*108.4 (±76.2)*	*129.1 (±88.3)*	*150.6 (±97.0)*	*180.3 (±115.3)*	*<0.001*
Apo A1 (mg/dl)	*121.0 (±22.6)*	*119.5 (±22.0)*	*117.5 (±21.5)*	*117.8 (±20.9)*	*<0.001*
Apo B (mg/dl)	*90.0 (±25.2)*	*97.7 (±25.6)*	*103.3 (±25.7)*	*108.9 (±26.8)*	*<0.001*
HOMA	*1.63 (±0.79)*	*1.71 (±0.85)*	*1.77 (±0.81)*	*1.96 (±0.90)*	*<0.001*
Insulin (μIU/ml)	*7.3 (±2.6)*	*7.5 (±2.9)*	*7.7 (±2.9)*	*8.5 (±3.3)*	*<0.001*
Waist	*73.29 (±8.3)*	*77.88 (±8.6)*	*82.64 (±7.4)*	*85.24 (±7.1)*	*<0.001*

SBP, systolic blood pressure (mmHg); DBP, diastolic blood pressure (mmHg); FBG, fasting serum glucose (mg/dl); TC, serum total cholesterol (mg/dl); LDL-C, serum low-densigty lipoprotein cholesterol (mg/dl); HDL-C, serum high-density lipoprotein cholesterol (mg/dl); TG, serum triglyceride (mg/dl); Apo A1, serum apolipoprotein A1 (mg/dl); Apo B, apolipoprotein B (mg/dl); Insulin, fasting serum insulin (μIU/ml); HOMA: homeostasis model assessment.

acid concentration, but was not statistically significant (p=0.054). In the third and fourth quartile, the ORs were 1.192 (95% CI 1.038–1.368, p=0.013) and 1.408 (95% CI 1.221–1.623, p<0.001), respectively, which were statistically significant increases for the incidence of hypertension in the group with high serum uric acid concentration (Table 5). On the other hand, multiple regression analysis using serum uric acid concentration as a continuous variable without dividing the subjects into 4 groups, gave statistically significant similar results for the relationship between hypertension and serum uric acid concentration (data not shown; p<0.001).

Correlation Between Serum Uric Acid Concentration and Insulin Resistance and the Risk Factors of Metabolic Syndrome

Even after adjusting for age, which probably affects BP, we found that for those with a high serum uric acid concentration there was a positive correlation with systolic and diastolic BP, fasting serum glucose, total cholesterol, serum low-density lipoprotein cholesterol, serum triglyceride concentration, serum Apo B, HOMA, fasting serum

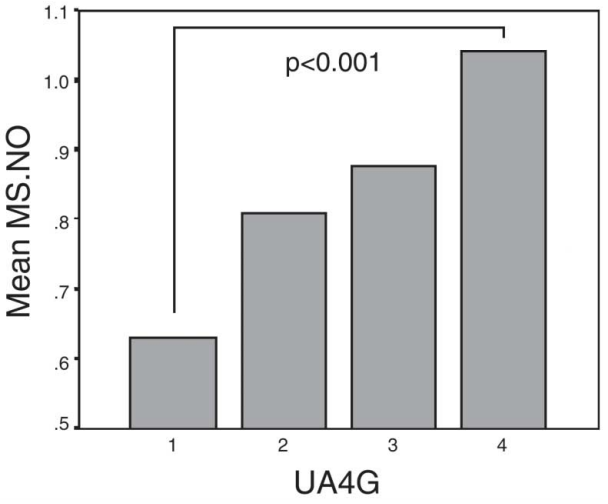

Fig 1. Number of metabolic syndrome variables by serum uric acid concentrations. UA4G, serum uric acid concentration quartiles group; Mean MS. NO, mean number of metabolic syndrome components.

insulin levels, and waist circumference. In addition, we detected an inverse correlation between serum uric acid concentration and pulse rate, and serum high-density lipoprotein cholesterol and serum Apo A concentrations (Table 6). On the other hand, when the study population was divided into serum uric acid quartiles, we found that as serum uric acid concentration increased the average number of items satisfying the NCEP-ATP Ⅲ definition of metabolic syndrome also increased (Fig 1).

Discussion

In the present study, we assessed the correlation between serum uric acid concentration, hypertension, insulin resistance and the risk factors for metabolic syndrome in a population of Korean adults who underwent a health screen. According to our results, when the study population was divided into quartiles based on serum uric acid concentration and factors that may affect BP and the serum uric acid concentration were ruled out, even for the group with a normal range of serum uric acid, the subgroup with a higher serum uric acid concentration had a higher incidence of hypertension; even when the men and women were analyzed separately, we obtained similar results. In addition, serum uric acid concentration was also found to be significantly correlated with the insulin resistance marker (HOMA), and the risk factors of metabolic syndrome. Moreover, serum uric acid concentrations were found to be positively correlated with the factor related to inflammation, hsCRP,[17] which has recently been reported to be an independent risk factor of hypertension. On the other hand, when the normal serum glucose group with a fasting serum glucose <110 mg/dl was analyzed separately, it was found that as fasting serum glucose concentration increased, the serum uric acid concentration also increased.

Serum uric acid increases BP by acting on the renal interstitium, which may damage the cardio- and cerebrovasculature. In patients with renal disease, increased serum uric acid concentrations and cardiovascular diseases are induced by the activation of the renin-angiotensin-aldosterone system. Waring et al reported that in normal individuals, injection of uric acid into the antecubital vein causes impaired vessel dilation by acetylcholine and impaired nitrogen oxide release by vascular endothelial cells,[18] thus indicating that uric acid per se is toxic to blood vessels.

There are numerous cross-sectional studies and prospective studies on serum uric acid concentration and the development of hypertension[6–9] One study has reported that when the serum uric acid concentration is higher than the initial baseline measurement by 3 mg/dl, mild hypertension developed in 87% of the study population.[10]

In relation to cardiovascular disease, patients with diabetes or hypertension, show suppressed activation of xanthine oxidase after an injection of allopurinol, which caused vascular endothelial cell-dependent dilatation of blood vessels,[19] suggesting that serum uric acid could be a direct marker of the progression of atherosclerosis. Patients who have received coronary artery bypass grafts,[20,21] and those with dilated cardiomyopathy,[22] show a reduction in cardiovascular complications after an injection of allopurinol, which suggests that serum uric acid concentration is closely associated with cardiovascular diseases. Although the mechanisms by which uric acid plays a pathogenetic role in cardiovascular disease is unclear, hyperuricemia is associated with deleterious effects on endothelial function, platelet adhesion and aggregation, or oxidative metabolism.[23] Thus, it has been recommended that the role of uric acid as a risk factor for cardiovascular disease and hypertension should be re-evaluated.[24]

In a large scale epidemiological study of the general population in Israel, Modan et al found that hyperinsulinemia was associated with an increase in serum uric acid concentration, and this finding was significant after adjusting for BMI, degree of impaired glucose tolerance, and serum triglyceride concentration.[25] In a study of 3,681 Japanese adult males an elevation of the serum uric acid concentration increased the risk of type 2 diabetes.[26] The inflammatory reaction also induces hypertension by a mechanism similar to that of serum uric acid. We found that hsCRP, which has previously been reported as an independent risk factor of hypertension, was positively correlated to serum uric acid concentration. In addition, there was a difference in serum uric acid concentration according to gender: they were lower in women than in men, possibly because of estrogen and other steroid hormones; this results concurs with those of previous reports.[27]

The NCEP-ATP Ⅲ in 2001 generated interest in metabolic syndrome. Both Costa et al[1] and Schmidt et al[28] reported a positive correlation between the risk factors of metabolic syndrome and serum uric acid concentration; however neither of the studies covered all 5 items used to define metabolic syndrome by the NCEP-ATP Ⅲ, and both were also small studies. The advantages of the present study is that the population was relatively large, 53,477 cases, and thus more likely to more closely resemble the general adult population. Moreover, the subjects were Asians, for whom data are lacking, and the study included all 5 NCEP-ATP Ⅲ risk factors of metabolic syndrome.

After dividing the study population into quartiles according to serum uric acid concentration, an independent association between an elevated serum uric acid concentration and hypertension, insulin resistance, and the risk factors of metabolic syndrome was detected in the group with normal range of serum uric acid concentration (the third quartile from the first). As shown by our results, even in the quartile with a normal range of serum uric acid concentration, the

average number of items that satisfied the risk factors of metabolic syndrome was increased (Fig 1). Thus, even in those with a normal serum uric acid concentration, careful follow-up may be required.

Study Limitations

First, this was a cross-sectional study, so the causal relationships between serum uric acid concentration and hypertension, insulin resistance and the risk factors of metabolic syndrome cannot be evaluated. Second, the study subjects volunteered for the health screen, which may have introduced a selection bias. Third, dietary habits may affect the serum uric acid concentration, but were not able to be investigated in the present study population and so could not be evaluated in relation to serum uric acid concentration. Fourth, there is no criterion for visceral obesity in Korea, so we used the standard waist circumference criterion for the Asian-Pacific region[16] and it would be interesting to repeat the analysis using the Japanese Society for the Study of Obesity criteria[29] because of the similarities in body stature of the Korean and Japanese peoples.

In conclusion, in the present Korean adult population, an elevated serum uric acid concentration was found to be independently correlated with hypertension, insulin resistance and the risk factors of metabolic syndrome. Even within the normal range of serum uric acid concentration, the risk of metabolic syndrome was found to be elevated in proportion to the serum uric acid concentration. However, to fully determine the nature of the causal relationship between serum uric acid concentration and the risk of metabolic syndrome, future prospective studies are required.

References

1. Costa A, Iguala I, Bedini J, Quinto L, Conget I. Uric acid concentration in subjects at risk of type 2 diabetes mellitus: Relationship to components of the metabolic syndrome. *Metabolism* 2002; **51:** 372–375.
2. Ryo M, Nakamura T, Kihara S, Kumada M, Shibazaki S, Takahashi M, et al. Adiponectin as a biomarker of the metabolic syndrome. *Circ J* 2004; **68:** 975–981.
3. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel Ⅲ). *JAMA* 2001; **285:** 2486–2496.
4. Sung KC, Kim BJ, Kim BS, Kang JH, Lee MH, Park JR, et al. In normoglycemic Koreans, insulin resistance and adipocity are independently correlated with high blood pressure. *Circ J* 2004; **68:** 898–902.
5. Saggiani F, Pilati S, Targher G, Branzi P, Muggeo M, Bonora E. Serum uric acid and related factors in 500 hospitalized subjects. *Metabolism* 1996; **45:** 1557–1561.
6. Klein R, Klein BE, Cornoni JC, Maready J, Cassel JC, Tyroler HA. Serum uric acid: Its relationship to coronary heart disease risk factors and cardiovascular disease in Evans County, Georgia. *Ann Intern Med* 1973; **132:** 401–410.
7. Kahn HA, Medalie JH, Neufeld HN, Riss E, Goldbourt U. The incidence of hypertension and associated factors: The Israel ischemic heart disease study. *Am Heart J* 1972; **84:** 171–182.
8. Selby JV, Friedman GD, Queensberry CP. Precursors of essential hypertension: Pulmonary function, heart rate, uric acid, serum cholesterol, and other serum chemistries. *Am J Epidemiol* 1990; **131:** 1017–1027.
9. Jossa F, Farinaro E, Panico S, Krogh V, Celentano E, Galasso R, et al. Serum uric acid and hypertension: The Olivetti heart study. *J Hum Hypertens* 1994; **8:** 677–681.
10. Zavaroni I, Mazza S, Fantuzzi M, Dall'Aglio E, Bonora E, Delsignore R, et al. Changes in insulin and lipid metabolism in males with asymptomatic hyperuricaemia. *J Intern Med* 1993; **234:** 25–30.
11. Vuorinen-Markkola H, Yki-Jarvinen H. Hyperuricemia and insulin resistance. *J Clin Endocrinol Metab* 1994; **78:** 25–29.
12. Cigolini M, Targher G, Tonoli M, Manara F, Muggeo M, De Sandre G. Hyperuricaemia: Relationship to body fat distribution and other components of the insulin resistance syndrome in 38-year-old healthy men and women. *Int J Obes Relat Metab Disord* 1995; **19:** 92–96.
13. Curb JD, Ford C, Hawkins CM, Smith EO, Zimbaldi N, Carter B, et al. A coordinating center in a clinical trial: The hypertension detection and follow up program. *Control Clin Trials* 1983; **4:** 171–186.
14. Himmelmann A, Kjeldsen SE, Hedner T. Recent hypertension guidelines: JNC-7 and ESH/ESC. *Blood Press* 2003; **12:** 196–197.
15. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostatic model assessment: Insulin resistance and β-cell function from fasting plasma glucose and insulin concentration in man. *Diabetologia* 1985; **28:** 412–419.
16. WHO West Pacific Region. The Asia-Pacific perspective: Redefining obesity and its treatment. *IOTF Feb* 2000 (report).
17. Sung KC, Suh JY, Kim BS, Kang JH, Kim H, Lee MH, et al. High sensitivity C-reactive protein as an independent risk factor for essential hypertension. *Am J Hypertens* 2003; **16:** 429–433.
18. Waring WS, Webb DJ, Maxwell SRJ. Effect of local hyperuricemia on endothelial function in the human forearm vascular bed. *Br J Clin Pharmacol* 2000; **49:** 511.
19. Linder L, Kiowski W, Buhler FR, Luscher TF. Indirect evidence for release of endothelium-derived relaxing factor in human forearm circulation in vivo: Blunted response in essential hypertension. *Circulation* 1990; **81:** 1762–1767.
20. Johnson WD, Kayser KL, Brenowitz JB, Saedi SF. A randomized controlled trial of allopurinol in coronary bypass surgery. *Am Heart J* 1991; **121:** 20–24.
21. Tabayashi K, Suzuki Y, Nagamine S, Ito Y, Sekino Y, Mohri H. A clinical trial of allopurinol (Zyloric) for myocardial protection. *J Thorac Cardiovasc Surg* 1991; **101:** 713–718.
22. Cappola TP, Kass DA, Nelson GS, Berger RD, Rosas GO, Kobeissi ZA, et al. Allopurinol improves myocardial efficiency in patients with idiopathic dilated cardiomyopathy. *Circulation* 2001; **104:** 2407–2411.
23. Alderman M, Redfern JS. Serum uric acid: A cardiovascular risk factor? *Ther Umsch* 2004; **61:** 547–552.
24. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovacular and renal disease? *Hypertension* 2003; **41:** 1183–1190.
25. Modan M, Halkin H, Karasik A, Lusky A. Elevated serum uric acid: A facet of hyperinsulinaemia. *Diabetologia* 1987; **30:** 713–718.
26. Nakanishi N, Okamoto M, Yoshida H, Matsuo Y, Suzuki K, Tatara K. Serum uric acid and risk for development of hypertension and impaired fasting glucose or type Ⅱ diabetes in Japanese male office workers. *Eur J Epidemiol* 2003; **18:** 523–530.
27. Sumino H, Ichikawa S, Kanda T, Nakamura T, Sakamaki T. Reduction of serum uric acid by hormone replacement therapy in postmenopausal women with hyperuricaemia. *Lancet* 1999; **354:** 650.
28. Schmidt MI, Watson RL, Duncan BB, Metcalf P, Brancati FL, Sharrett AR, et al. Clustering of dyslipidemia, hyperuricemia, diabetes, and hypertension and its association with fasting insulin and central and overall obesity in a general population. *Metabolism* 1996; **45:** 699–706.
29. The Examination Committee of Criteria for Obesity Disease in Japan; Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. *Circ J* 2002; **66:** 987–992.