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Metabolic

Serum Uric Acid Is a Determinant of Metabolic Syndrome in a Population-Based Study

Altan Onat, Hüseyin Uyarel, Gülay Hergenç, Ahmet Karabulut, Sinan Albayrak, Ibrahim Sarı, Mehmet Yazıcı, and Ibrahim Keleş

Background: Determination of serum uric acid concentrations and role in risk of metabolic syndrome (MS) were investigated in 1877 participants in a cross-sectional population-based study including a brief follow-up.

Methods: The MS was identified by modified criteria of the Adult Treatment Panel III, and coronary heart disease (CHD) by clinical findings and Minnesota coding of resting electrocardiograms. Uric acid concentrations were measured by the uricase method.

Results: Metabolic syndrome was present in 39.1% of the cohort. Linear regression analysis of uric acid levels in a model comprising 13 variables identified gender, waist girth, total cholesterol (TC), alcohol usage, triglycerides, log C-reactive protein (CRP), and log γ-glutamyl transferase (GGT), and in women diuretic use and elevated blood pressure (BP), as significant independent covariates whereby the largest contribution (1.6 mg/dL) was generated by waist girth. Logistic regression analysis of serum uric acid for MS disclosed for the top versus the bottom tertile an odds ratio (OR) of 1.89 (95% confidence interval [CI]: 1.45–2.46) in men and women combined, after ajustment for sex, age, TC, log CRP, log GGT, alcohol, and diuretic drug use, presence of diabetes/impaired fasting glucose, elevated BP, and smoking status. This corresponded to an increase by 35% in MS likelihood for each 1 SD uric acid increment. This rate declined to a significant 15% by inclusion of waist girth into the model. The OR of uric acid concentrations for prevalent and incident CHD, adjusted for age, MS, smoking, and diuretic use, was not significant among women and only tended toward significance in men.

Conclusions: Abdominal obesity is the main determinant of uric acid variance. An increment of 1 SD in serum uric acid levels are associated in both sexes with a 35% higher MS likelihood, independent of 10 risk factors related to MS. After adjustment for waist girth, a more modest but significant likelihood persists, which suggests that serum uric acid is a determinant of MS. Am J Hypertens 2006;19:1055–1062 © 2006 American Journal of Hypertension, Ltd.

Key Words: Abdominal obesity, coronary heart disease risk, hypertension, metabolic syndrome, population-based study, serum uric acid.

Substantial epidemiologic and experimental evidence exists that serum uric acid is an independent risk factor for cardiovascular disease, especially in hypertensive and diabetic individuals.[1–3] The issue, however, whether uric acid exerts its effect independent of established cardiovascular risk factors is still controversial.[4] Elevated levels of uric acid correlate with aging, male gender, hyperlipidemia, obesity, hyperinsulinemia, diabetes mellitus, and glucose intolerance[5,6] and mediate the accelerated progression of hypertension and development of end-organ injury.[7] Uric acid activates the complement system,[8] and in soluble form induces the development of oxidative stress and LDL oxidation.[8] Uric acid is proinflammatory in rat vascular smooth muscle cells and stimulates human mononuclear cells to produce cytokines.[7,9]

Uric acid concentrations have been related to individual components of the metabolic syndrome (MS) in subjects at risk of diabetes.[10] It has been shown in limited numbers of healthy or obese Japanese men that visceral adiposity assessed by computed tomography was the strongest contributor to elevation in uric acid concentrations and low uric acid clearance[11] and that subjects having visceral fat obesity with hyperuricemia were designated as an over-

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From the Turkish Society of Cardiology (AO), Cerrahpaşa Medical Faculty (AO, IK), Istanbul University, Istanbul; S. Ersek Cardiovascular Surgery Center (HU, AK, IS), Biology Department, Yildiz Technical University (GH), Istanbul; and Cardiology Department of I. Baysal U. Düzce Medical Faculty (SA, MY), Düzce, Turkey.

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Address correspondence and reprint requests to Prof. Dr. Altan Onat, Nisbetiye cad. 37/24, Etiler 34335, Istanbul, Turkey; e-mail: alt_onat@yahoo.com.tr

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production type.[12] However, information is scarce on the determinants of serum uric acid among diverse variables in the population at large, and with respect to its link to MS. Among Japanese individuals undergoing general health screening, it was reported that the prevalence of MS showed a graded increase in serum uric acid levels, and that in men with no MS these levels were an independent risk factor for incidence of carotid plaque.[13] The association with MS still needs to be delineated in other population samples.

Hence, the purpose of this cross-sectional analysis is to 1) describe the independent covariates of serum concentrations of uric acid, and 2) study the potential independence of uric acid levels and their contribution to the risk for MS, among male and female participants of the Turkish Adult Risk Factor Study. Such an analysis may be revealing, in view of the high prevalence of MS in Turkish adults[14] and the susceptibility of Turkish men to visceral adiposity.[15] The role of uric acid in the risk for cardiovascular disease will also be assessed.

Methods

Study Population

Participants of this study sample form the cohort of the Turkish Adult Risk Factor Study, a prospective survey on the prevalence of cardiac disease and risk factors in a representative sample of adults in Turkey carried out almost biennially throughout all geographic regions of the country.[16] Details of sampling were described previously.[17] Partial logistic support was provided by the Turkish Ministry of Health. This article is based on the survey 2003/04 at which subjects were aged 33 years or older (mean 53 ± 13 years). Individuals of the cohort were visited in their address on the eve of the examination and were asked to give written informed consent for participation the next morning. The response rate was 72.5%. Of the baseline study sample residents in Western Turkey, constituting half of the entire sample, were reexamined 2.1 years later. The survey conformed to the principles embodied in the Declaration of Helsinki and was approved by the Istanbul University ethics committee. Data were obtained by history of the past years by a questionnaire, physical examination of the cardiovascular system, and recording of a resting electrocardiogram (ECG). Antihypertensive medications were used by 24.4%; lipid-lowering drugs by just over 2% of participants. Diuretic drug usage (thiazide, indapamide, and furosemide) was reported in 69 persons (3.7% of sample).

Measurement of Risk Variables

Blood pressure (BP) was measured with an aneroid sphygmomanometer (Erka, Kallmeyer Medizintechnik GmbH, Germany) in the sitting position on the right arm, and the mean of two recordings 3 min apart was recorded. Waist circumference was measured to the nearest 1 cm, with the subject standing and wearing only underwear, at the level midway between the lower rib margin and the iliac crest. With regard to cigarette smoking, nonsmokers, past smokers, and current smokers formed the categories. Anyone who drank alcoholic drinks once a week or more frequently was considered as user of alcoholic drinks, and those who drank less frequently were classified with the nondrinkers. Physical activity was graded by the participant himself into four categories of increasing order with the aid of a scheme.[17]

Blood samples were collected in an 11-h or longer fasting state in this study, except postprandially in 19% of individuals. Samples were shipped on cooled gel packs at 2° to 5°C to Istanbul to be stored in deep-freeze at −75°C, until analyzed at the Yıldız Technical University. Serum concentrations of uric acid were determined enzymatically (uricase) by InfinityTM (Thermo Electron, Victoria, Australia) kit using the modified Trinder method with a Hitachi (Tokyo, Japan) 902 autoanalyzer. Interassay and intraassay coefficient of variation (CV) for first and second step controls for uric acid were <2.4% and <1.9%, respectively. Concentrations of total cholesterol, fasting triglycerides, glucose, and HDL-cholesterol (HDL-C plus second generation, directly without precipitation) were determined by using enzymatic kits from Roche Diagnostics (Mannheim, Germany). The LDL-cholesterol values were computed according to the Friedewald formula. Serum γ-glutamyl transferase (GGT) activity was assayed by the kinetic method using Glucana as substrate (Thermo Trace, Noble Park, Victoria, Australia). Serum concentrations of C3, C-reactive protein (CRP), and apolipoprotein B were measured by Behring kits and nephelometry (BN Prospec, Behring Diagnostics, Westwood, MA). Concentrations of insulin were determined by the chemiluminescent immunometric method using Roche kits and Elecsys 1010 immunautoanalyzer (Roche Diagnostics).

Metabolic syndrome was identified when three of the five criteria of the National Cholesterol Education Program (NCEP) (ATP III)[18] were met, modified for prediabetes (fasting glucose ≥100 mg/dL).[19] These criteria were further modified for abdominal obesity using cutpoints of ≥95 cm in men and ≥91 cm women, as recently assessed in the Turkish Adult Risk Factor study (Onat A et al. Atherosclerosis 2006; in press). For HDL-cholesterol in women, the threshold of <45 mg/dL rather than <50 mg/dL was chosen in view of prevailing genetic low HDL-cholesterol levels in this population. Missing data on triglycerides did not preclude the identification of MS as availability of no more than three criteria was required, and participants meeting one and three or more criteria could be decided. In the remaining few instances fasting values of the previous survey participation were taken into account. Elevated BP is used in this article to denote ≥130/85 mm Hg, the NCEP criterion in the context of MS. Type 2 diabetes was diagnosed with the criteria of the American Diabetes Association,[19] namely by self report or when plasma fasting glucose was ≥126 mg/dL or when

2-h postprandial glucose was >200 mg/dL, and impaired fasting glucose (IFG) denoted fasting glucose values of 100 to 125 mg/dL. Homeostatic model assessment (HOMA) was calculated with the following formula[20]: Insulin (mIU/L) × Glucose (in mmol/L)/22.5.

Diagnosis of coronary heart disease (CHD) was based on the presence of angina pectoris, of a history of myocardial infarction with or without accompanying Minnesota codes of the ECG,[21] or on a history of myocardial revascularization. Among women typical angina and age >45 years were prerequisite for a diagnosis when angina was isolated. The ECG changes of "ischemic type" of greater than minor degree (codes 1.1-2, 4.1-2, 5.1-2, 7.1) were considered as myocardial infarct sequelae or myocardial ischemia, respectively.

Data Analysis

Because the distribution of GGT, HOMA, CRP, and insulin is skewed, values derived from log-transformed (geometric) means were used. Pearson correlation tests were made for two sets of values. Uric acid cutpoints of 5.2 and 6.5 mg/dL in men, and 4.0 and 5.1 mg/dL in women determined the tertiles.

Multiple linear regression analyses were performed with continuous parameters, whereby variables with skewed distribution were log-transformed. The MS and CHD likelihood estimates and 95% confidence intervals (CI) were obtained by use of logistic regression analyses in models that controlled for confounders. The contribution of a significant independent variable as a determinant of uric acid in a linear regression analysis was estimated by multiplying the related mean value of the variable with the β coefficient. Statistical analyses were performed using SPSS-10 for Windows (SPSS, Inc., Chicago, IL). A value of $P < .05$ on the two-tail test was considered statistically significant.

Results

Metabolic syndrome was identified in 358 men (39.1%) and 376 women (39.1%). The brief follow-up resulted in 1680 person-years, during which 6 incident CHD deaths and 26 nonfatal CHD were diagnosed to have newly developed, which, along with those having CHD at baseline, resulted in 219 participants with fatal or nonfatal CHD (11.7%).

Characteristics of the sample population (mean age, 53 years) are presented in Table 1 by gender and presence of MS. A tendency to abdominal obesity, high serum triglycerides, and low levels of total, HDL-, and LDL-cholesterol when compared with Western populations may be noted. Subjects with MS differed significantly from the rest of the cohort in all studied risk parameters except for LDL-cholesterol level and alcohol usage. Mean serum uric acid values in participants with MS exceeded by 12% those without MS.

Mean values of serum uric acid were 5.97 ± 1.46 mg/dL (355 ± 87 μmol/L) in 915 men, and 4.69 ± 1.28 mg/dL (278 ± 76 μmol/L) in 962 women ($P < .001$). Values were significantly correlated with age ($r = 0.24$) only in women. Table 2 shows the bivariate correlations of various parameters with uric acid. Highly significant correlations (with coefficients $r = 0.17$ to 0.27) existed in both genders between uric acid and serum total cholesterol, triglycerides, log GGT, complement C3, log CRP, log insulin, waist circumference, and body mass index (BMI). Weaker correlations ($r = \sim 0.1$) were noted with systolic BP, physical activity grade, and in women with apolipoprotein B.

Determinants in Multivariate Analyses

In a linear regression model including uric acid as dependent parameter and an additional 13 variables among 1492 persons, gender, waist circumference, serum levels of total cholesterol, triglycerides, alcohol intake, GGT, and CRP emerged as significant independent covariates, whereas age, smoking status, and physical inactivity were not independently associated significantly (Table 3).

According to the regression equation, nearly one-third of the contribution to the variability of serum uric acid in the study group derived (1.61 mg/dL) from waist circumference. Male gender, total cholesterol, alcohol and diuretic use, presence of elevated BP, triglyceride, and GGT levels, lent the remaining important independent contributions.

Odds Ratios of Uric Acid for Metabolic Syndrome

Associations of uric acid tertiles for MS (680 cases) among 1738 men and women were analyzed in a basic logistic regression model (model 1, Table 4), which included age, alcohol intake, diuretic use, smoking status, total cholesterol, and log CRP as independent variables. Serum uric acid top tertile exhibited a roughly twofold significant odds ratio (OR) for MS likelihood compared with the bottom tertile, in men and women alike. Additional three regression models sought to differentiate whether this likelihood was independent of certain components of MS or of serum GGT, also linked with MS, and if not, which variable abolished the association with uric acid. Adjustment for two components of MS (model 2) or adding log GGT (model 3) did not essentially change this significant association. Introduction of waist circumference as a continuous variable abolished the significance of uric acid tertiles in men (OR 1.15) and substantially weakened the OR to a borderline significant ($P = .054$) 1.51 in women. Nonetheless, a significant OR 1.35 (95% CI: 1.01–1.81) was retained in the entire sample.

The mean uric acid gradient across the upper and lower tertiles was 2.16-fold SD in men and 2.13-fold SD in women. The calculated corresponding ORs among adults for an increment of 1 SD uric acid ranged from 1.39 in model 1 to 1.15 in model 4.

Table 1. Characteristics of sample population by gender and presence of metabolic syndrome

		Men (*n* = 915)		Women (*n* = 962)			No MS (*n* = 1143)		MS (*n* = 734)		
	n	**Mean**	**SD**	**Mean**	**SD**	***P*<**	**Mean**	**SD**	**Mean**	**SD**	***P*<**
Age (y)	1877	53.0	11	52.5	10.6	ns	50.8	10.8	55.7	10.2	.001
Body mass index (kg/m^2)	1877	27.9	4.4	30.7	5.6	.001	27.7	4.6	31.9	5.1	.001
Waist circumference (cm)	1875	95.4	10.9	94.4	12.3	.050	90.4	10.7	101.9	9.4	.001
Systolic blood pressure (mm Hg)	1854	124	20	129	22	.001	120	18	136	21	.001
Diastolic blood pressure (mm Hg)	1854	80	11	81	11	.001	77	10	85	10	.049
Complement C3 (g/L)	1323	1.29	0.27	1.34	0.28	.001	1.23	0.24	1.45	0.27	.001
Log C-reactive protein (mg/L)*	1761	1.93	3.03	2.46	3.16	.001	2.02	3.12	3.46	2.89	.001
Uric acid (mg/dL)	1877	5.97	1.46	4.69	1.28	.001	5.08	1.42	5.68	1.6	.001
Log gamma GT (U/L)*	1873	26.8	1.85	18.6	1.87	.001	23.5	1.8	29.4	1.8	.001
Log fasting insulin (mIU/L)*	1181	7.58	2.0	7.79	1.83	.22	6.49	1.82	9.79	1.86	.001
Total cholesterol (mg/dL)	1859	189.1	39.2	201.3	42	.001	191.8	39.8	200.9	42.6	.001
HDL-cholesterol (mg/dL)	1860	39.5	11.1	47.5	12.6	.001	46.8	12.8	38.6	10.2	.001
LDL-cholesterol (mg/dL)	1611	111.4	34	121	35.8	.001	116	34.2	117.3	36.9	.44
Fasting triglycerides (mg/dL)	1612	196.7	126.9	164.7	91.9	.001	144.9	86.4	232.2	122	.001
Fasting glucose (mg/dL)	1611	98.9	37.6	97.9	40	.61	91.2	31.2	109.2	46.2	.001
Log HOMA*	1178	1.72	2.17	1.80	2.05	.28	1.41	1.93	2.51	2.08	.001
Apolipoprotein B (mg/dL)	970	105.8	30	104.3	29	.42	100.2	29.4	112.4	35	.001
Physical activity grade I–IV	1838	2.39	0.78	2.06	0.61	.001	2.28	0.72	2.13	0.71	.001
Current smoker (%)	1877	43.6		14.8		.001	33.4		21.8		.001
Former smoker (%)	1877	27.8		3.6		.001	14.4		16.9		ns
Alcohol usage (%)	1877	15.0		0.8		.001	7.7		7.8		ns

CRP = C-reactive protein; GT = glutamyl transferase.

* Mean ± SD denote values derived from log-transformed means and SD.

Table 2. Pearson correlation coefficients (*r*) between serum uric acid and 18 risk parameters in Turkish adults

	Men			Women		
	n	***r***	***P***	***n***	***r***	***P<***
Age (y)	915	0.026	.42	962	0.235	.001
Waist circumference (cm)	914	0.269	.001	961	0.306	.001
Body mass index (kg/m^2)	900	0.229	.001	947	0.273	.001
Log gamma GT	912	0.263	.001	961	0.189	.001
Complement C3 (g/L)	610	0.182	.001	713	0.245	.001
Triglycerides (mg/dL)	761	0.181	.001	851	0.236	.001
Log insulin	522	0.168	.001	659	0.186	.001
Total cholesterol (mg/dL)	905	0.166	.001	954	0.287	.001
LDL-cholesterol (mg/dL)	760	0.073	.044	851	0.209	.001
Apolipoprotein B (mg/dL)	452	0.085	.15	518	0.115	.009
Log C-reactive protein	860	0.129	.001	901	0.305	.001
Fasting glucose (mg/dL)	705	−0.125	.001	832	0.011	.74
Systolic pressure (mm Hg)	901	0.085	.011	953	0.18	.001
Physical activity grade	897	−0.085	.011	941	−0.131	.001
Fibrinogen (g/L)	198	−0.147	.039	222	0.192	.004
Alcohol usage	915	0.152	.001	962	−0.014	.66
Smoking status	915	−0.04	.23	964	−0.053	.097
HDL-cholesterol (mg/dL)	905	−0.038	.25	955	0.002	.95

Association With Coronary Disease

The association with CHD likelihood was analyzed with sex-specific cutpoints for the top uric acid tertile of 6.5 and 5.1 mg/dL in men and women, respectively (Table 5). For 218 cases of prevalent and incident CHD, the OR across the tertiles adjusted for gender, age, MS, smoking status, and diuretic use was not significant in women. Among men, the multiadjusted OR tended to a borderline significant value of 1.50 (95% CI 0.88–2.56; $P = .14$).

Discussion

In this population-based study, waist circumference was the major determinant of the variability in serum uric acid concentrations, and uric acid levels displayed a high OR for MS, after adjustment for 10 major parameters including impaired glucose regulation and elevated BP, which retained significance, especially in women, despite attenuation after adjustment for the powerful waist circumference.

Link of Serum Uric Acid With Abdominal Obesity and Inflammation

Multivariate analysis indicated that waist circumference contributed 1.6 mg/dL to concentrations of uric acid, independent of 13 other variables including alcohol and diuretic use, elevated BP, impaired glucose regulation, and GGT. In studies conducted in men in East Asia investigating the factors for the development of hyperuricemia, BMI and serum triglycerides had been delineated as independent determinants.[22,23] A positive correlation between

Table 3. Determinants of serum uric acid in linear regression, by gender

	Adults (*n* = 1492)			Men (*n* = 709)			Women (*n* = 783)		
	β coef.	**SE**	***P***	**β coef.**	**SE**	***P***	**β coef.**	**SE**	***P***
Sex (M)	1.28	0.085	.001						
Waist circumference (cm)	0.017	0.003	.001	0.022	0.005	.001	0.012	0.004	.004
Total cholesterol (mg/dL)	0.004	0.001	.001	0.0023	0.001	.12	0.0052	0.001	.001
Alcohol use (y/n)	0.449	0.138	.001	0.403	0.154	.009	0.479	0.494	.33
Diuretic use (y/n)	0.386	0.177	.030	0.35	0.311	.26	0.407	0.207	.050
BP ≥130/85 mm Hg (y/n)	0.259	0.077	.001	0.225	0.123	.068	0.281	0.096	.003
Triglycerides (mg/dL)	0.0012	0.000	.001	0.0014	0.000	.002	0.00078	0.001	.12
Log gamma GT	0.587	0.133	.001	0.835	0.21	.001	0.353	0.169	.036
Log C-reactive protein	0.334	0.071	.001	0.255	0.109	.001	0.414	0.094	.001
Age (y)	0.0038	0.003	.27	0.0013	0.005	.80	0.0066	0.005	.16
Diabetes/IFG (y/n)	−0.136	0.08	.091	−0.405	0.121	.001	0.145	0.106	.17
Physical activity grade I–IV	−0.06	0.049	.22	−0.04	0.066	.59	−0.129	0.074	.083
Smoking status	−0.02	0.046	.64	−0.07	0.067	.31	−0.041	0.063	.51

Model in adults was significant ($F = 55.1$, $P < .001$) and explained 32% of variance.

Table 4. Uric acid tertiles and likelihood of metabolic syndrome in four logistic regression models

	1		2		3		4	
Model	**OR**	**95% conf.int.**	**OR**	**95% conf.int.**	**OR**	**95% conf.int.**	**OR**	**95% conf.int.**
Adults (n = 1738)								
Uric acid tertile 2	1.44	1.11–1.87	1.55	1.47–5.34	1.40	1.07–1.82	1.19	0.89–1.59
Uric acid tertile 3	2.02	1.55–2.63	1.97	1.44–2.70	1.89	1.45–2.46	1.35	1.01–1.81
Log C-reactive protein	2.26	1.81–2.83	2.03	1.57–2.64	2.09	1.67–2.62	1.56	1.21–2.01
Diabetes/IFG			8.39	6.18–11.4				
BP ≥130/85 mm Hg			9.99	7.53–13.24				
Log gamma GT					2.65	1.75–4.02		
Waist circumference (cm)							1.12	1.10–1.13
Men (n = 850)								
Uric acid tertile 2	1.44	1.01–2.06	1.68	1.10–2.59	1.43	1.00–2.05	1.06	0.70–1.60
Uric acid tertile 3	1.89	1.32–2.71	2.17	1.40–3.36	1.75	1.21–2.53	1.15	0.76–1.74
Log C-reactive protein	1.68	1.24–2.28	1.73	1.21–2.48	1.59	1.17–2.16	1.24	0.86–1.78
Diabetes/IFG			7.75	5.10–11.8				
BP ≥130/85 mm Hg			10.9	7.22–16.5				
Log gamma GT					2.29	1.27–4.13		
Waist circumference (cm)							1.14	1.12–1.17
Women (n = 888)								
Uric acid tertile 2	1.45	0.98–2.13	1.41	0.89–2.25	1.37	0.93–2.03	1.31	0.87–1.99
Uric acid tertile 3	2.03	1.37–2.99	1.69	1.07–2.69	1.94	1.31–2.87	1.51	0.993–2.31
Log C-reactive protein	3.05	2.17–4.28	2.32	1.57–3.43	2.75	1.95–3.88	2.00	1.21–3.3
Diabetes/IFG			9.36	5.87–14.9				
BP ≥130/85 mm Hg			9.56	6.42–14.24				
Log gamma GT					2.85	1.57–5.17		
Waist circumference (cm)							1.09	1.07–1.11

IFG = impaired fasting glucose.
All models include sex, age, smoking status, alcohol usage, diuretic use, and total cholesterol.
MS existed in 333 men (39.2%) and 347 women (39.1%), diuretic use in 25 men and 43 women.
Uric acid top tertile ≥6.5 mg/dL in men, ≥5.1 mg/dL in women.

hyperuricemia and hyperinsulinemia, independent of triglycerides, glucose, BP, and obesity, was noted in a cross-sectional study on nondiabetic Taiwanese adults,[24] as were total cholesterol concentrations. We obtained evidence that both CRP and waist circumference emerged as independent covariates of uric acid. Visceral adiposity contributed importantly to uric acid levels, which have the capacity to induce inflammatory and vascular mechanisms, as borne out by experimental evidence.[9] In our multivariate analysis, serum uric acid and elevated BP were associated with each other, after adjustment for possible confounders. Uric acid may induce endothelial dysfunction, which has been ascribed as a major pathogenetic mechanism in mediating hypertension, by way of impaired nitrous oxide release and activation of circulating platelets.[9]

An independent relationship between hyperuricemia and triglycerides was reported in the Coronary Artery Risk

Table 5. Association between uric acid tertiles and CHD adjusted for risk factors

	Adults (n = 1876)		Men (n = 915)		Women (n = 961)	
	OR	**95% conf.int.**	**OR**	**95% conf.int.**	**OR**	**95% conf.int.**
Sex (M)	0.87	0.60; 1.26				
Uric acid tertile 2	1.19	0.80; 1.76	1.18	0.80; 1.76	1.18	0.68; 2.06
Uric acid tertile 3	1.21	0.83; 1.77	1.50	0.88; 2.56	0.96	0.56; 1.66
Age (y)	1.077	1.06; 1.09	1.068	1.047; 1.09	1.092	1.07; 1.12
Metabolic syndrome	2.27	1.67; 3.10	2.51	1.63; 3.89	1.96	1.25; 3.08
Current smoker	1.32	0.85; 2.04	1.40	0.80; 2.46	1.25	0.58; 2.69
Past smoker	1.58	1.004; 2.49	1.73	1.013; 2.96	1.32	0.42; 4.11
Diuretic usage	1.51	0.82; 2.77	3.11	1.29; 7.53	0.85	0.35; 2.07

Included in model were 109 fatal and nonfatal CHD in each gender, and 358 and 376 subjects with MS in men and women, respectively.
Uric acid top tertile ≥6.5 mg/dL in men, ≥5.1 mg/dL in women.

Development in Young Adults (CARDIA) study among 4053 young African American and white men.[24] In the regression model of the present study, triglycerides, although proving an independent determinant of serum uric acid, contributed modestly when a variety of variables such as total cholesterol, waist girth, GGT, CRP, elevated BP, and physical activity were included. The lack of correlation between uric acid and HDL-cholesterol levels may be attributed both to a genetic component of low HDL levels and to the latter's poor correlation with insulin resistance among Turks.

In line with the knowledge that alcohol usage lowers urate excretion[25] and increases urate generation,[26] alcohol intake did emerge in this population sample as an independent determinant of uric acid values.

Independent Excess Odds Ratio of Uric Acid for Metabolic Syndrome

The present study estimated quantitatively the risk of uric acid levels for the likelihood of MS in a middle-aged and elderly population sample. An OR of 1.35 in adults was elicited for each increment of 1 SD uric acid, after adjustment for age, smoking, alcohol intake, total cholesterol, diuretic drug administration, CRP, and two major components of MS. Abdominal obesity, the central component of MS, reduced this association by more than one-half, but a modest (OR 1.15 per 1 SD of uric acid), although significant, MS likelihood persisted. This demonstrates an independent link of uric acid levels with MS, tighter in women. In men, hyperuricemia's link to MS was weaker due to a stronger link between central obesity and MS. The magnitude these levels confer risk for MS is in general keeping with the new analysis on Japanese[13] in whom ORs of 1.26 and 1.71 were reported in men and women, respectively, per 1 mg/dL increase in uric acid level, especially considering that our model also adjusted for other risk factors.

An interesting difference between Japanese and Turkish adults manifested as opposite effects of cigarette smoking on the enhancement of MS. Although current smoking was found as a risk factor with an approximately twofold OR for MS among Japanese men and women, it was "protective" from MS with a significant OR of 0.75 (in model 2) in Turks, because smoking protects from abdominal obesity in Turks. This further stresses abdominal obesity as the driving element for MS.

It has been hypothesized that increases in the serum level of the antioxidant uric acid might counteract oxidative damage in subjects with atherosclerosis, based on the observation that individuals who developed carotid intima–media thickness had higher serum total antioxidant capacity than matching controls with low thickness.[27] Although epidemiologic studies per se are unable to resolve the cause of the covariation between cardiovascular risk factors and uric acid in multivariate analyses,[28] our findings are at variance with this hypothesis and favor hyperuricemia as a risk factor for MS. Uric acid retained its independent association with MS, regardless of elevated BP, impaired glucose regulation, and CRP being included in the model. The association's significance was attenuated only (without disappearing) by the addition of the variable of abdominal obesity.

In this study the demonstration of abdominal obesity as the major determinant of serum uric acid in the general population and of increasing uricemia independently imparting excess risk for MS supports the concept that obesity-associated MS is accompanied by hyperuricemia.[29]

Serum Uric Acid, A Possible Independent Marker of CHD Likelihood in Men Only?

Sex-specific tertiles of uricemia did not prove to be significantly associated with CHD likelihood among women and only tended to borderline significance in men, when adjusted for the presence of MS, age, smoking, and diuretic use. The possible CHD risk of modest magnitude is in general agreement with the result of a new meta-analysis on serum uric acid and CHD (involving more than 9000 incident cases and more than 150,000 controls).[30] Baseline serum uric acid values in the top third of the population had about a 10% greater risk of CHD than those in the bottom third, after adjustment for possible confounders.

Our findings, taken as a whole, indicate that the significant relationship between serum uric acid and MS is partly independent of abdominal obesity in women in whom the MS risk contains all the CHD risk conferred by hyperuricemia. In contrast in men, hyperuricemic concentrations exhibit an association with MS only inasmuch as they reflect abdominal obesity, yet an association of uric acid with CHD, independent of MS cannot be ruled out—conceiveably in individuals with insulin resistance but no MS, a constellation more commonly encountered in men. These observations are in essential agreement with the findings in the prospective Chin-Shan Community Study,[31] in which multiadjusted CHD events were significantly predicted by hyperuricemia in women alone, and uric acid had a significant role for CHD only in high-risk groups such as MS.

This study is limited by its cross-sectional nature with regard to the assessment of MS risk, yet it has the strength of being based on a representative population sample of both sexes. Furthermore, the present analysis involves the most comprehensive adjustments made regarding the relationship between hyperuricemia and MS, being controlled even for MS components, diuretic administration, GGT, and CRP.

We conclude that the variance in serum uric acid levels in a general population is affected by gender, concentrations of lipids, GGT, CRP, and, foremost, by waist circumference. An increment of 1 SD in serum uric acid levels are associated in both sexes with a 35% higher MS likelihood, independent of age, smoking, alcohol use, di-

uretic administration, total cholesterol, GGT, CRP values, elvated BP, and impaired glucose regulation. The significance of increased likelihood persists but diminishes to 15% when abdominal obesity, the central component of MS, is controlled.

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