# Is Hyperuricemia Another Facet of the Metabolic Syndrome?

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**Background:** Hyperuricemia is commonly associated with obesity, glucose intolerance, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. The resemblance of the metabolic syndrome and hyperuricemia has led to the suggestion that hyperuricemia is a part of the metabolic syndrome. The purpose of this study is to examine the contribution of uric acid (UA) as an additional component of the metabolic syndrome in middle-aged men.

**Methods:** In total, 393 male participants, aged 45–60 years, were recruited from a professional health evaluation program. Anthropometric measurements and blood pressure (BP) were taken after an overnight fast. Fasting blood samples were collected for the measurements of glucose, UA, and lipid profile. Logistic regression models were fitted to examine the relationship between UA and the diagnosis of metabolic syndrome. Factor analysis was performed to explore the relationship between UA and the components of the metabolic syndrome.

**Results:** The diagnosis of the metabolic syndrome was significantly associated with waist circumference (WC), glucose, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), systolic BP, and liver enzyme levels, but not associated with UA levels. The sensitivity of hyperuricemia (serum UA ≥ 7.0 mg/dL) for the diagnosis of the metabolic syndrome was 58.0% and the specificity was 55.3%. In factor analysis, UA aggregated with body mass index, WC, glucose, log TG, and HDL-C as a metabolic factor. Systolic and diastolic BP were loaded on a second factor separately. The model loaded with UA explained a similar proportion of the total variance (56.9%), as did the model loaded without UA (62.5%).

**Conclusion:** Our results suggest that the contribution of UA as an additional component of the syndrome seems to be insignificant. We propose that hyperuricemia might not be an important facet for the understanding of the underlying structure of the metabolic syndrome. [*J Chin Med Assoc* 2006;69(3):104–109]

**Key Words:** factor analysis, hyperuricemia, metabolic syndrome, obesity

## Introduction

Hyperuricemia is commonly seen in association with obesity, dyslipidemia, glucose intolerance, and hypertension,[1,2] a cluster of metabolic risk factors that characterize the metabolic syndrome.[3] Lakka et al[4] reported that cardiovascular mortality was increased 2–3-fold in middle-aged men with the metabolic syndrome. Several studies have shown that increased serum uric acid (UA) levels were also associated with risk for cardiovascular disease.[5,6] The resemblance of hyperuricemia and the metabolic syndrome has led to the suggestion that the metabolic syndrome can be further expanded to include hyperuricemia.[7,8] However, the role of UA in the diagnosis of the metabolic syndrome has not been established. The recent revised version for the diagnosis of the metabolic syndrome from the Adult Treatment Panel III (ATP III) of the

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National Cholesterol Education Program (NCEP) has identified several components, which did not include hyperuricemia.[3] Bonora et al[9] suggested that obesity played a major role in linking hyperuricemia with cardiovascular risk factors. Clausen et al[10] found that the association between UA and the metabolic syndrome might be secondary to the association with dyslipidemia. Since most persons with the metabolic syndrome in clinical practice carry multiple risk factors,[3] we hypothesize that hyperuricemia may not be required for the diagnosis of the metabolic syndrome. The purpose of this study is to examine the contribution of UA as an additional component of the metabolic syndrome in middle-aged men. We are also interested in investigating patterns underlying the co-occurrence of components of the metabolic syndrome by using factor analysis.

## Methods

### *Subjects*

From October 2002 to January 2003, 393 middle-aged Chinese men were recruited for this study consecutively from the Clinical Prevention Service Program at the Taipei Veterans General Hospital (VGH), a university teaching hospital with 2,700 inpatient beds. It is a professional health evaluation program with more than 8,000 participants per year. About 500 male participants, aged 45–60 years, were registered during the study period. We excluded the patients with known history of diabetes or with hypertension under medical control. Those with fasting plasma glucose (PG) higher than 126 mg/dL were also excluded from the study. The eligible participants were subjected to clinical examinations after a 10-hour overnight fast.

### *Clinical examinations*

Each subject received anthropometric measurements performed by the same group of technicians at 08:00.[11] Body height (BH) was measured to the nearest millimeter, and body weight (BW) was measured to the nearest 0.1 kg. Body mass index (BMI) was calculated as BW divided by BH squared (kg/m$^2$). Waist circumference (WC) was measured at the level of the umbilicus to the nearest millimeter by an anthropometric tape (kp 1508; King-Life, Taipei, Taiwan). Supine blood pressure (BP) was taken twice after 10 minutes of rest by a sphygmomanometer (Baumanometer; W. A. Baum Co Inc, Copiague, NY, USA) at 1-minute intervals.[12] The sphygmomanometer was used with an initial pressure of 30 mmHg above the pulse obliteration pressure and the systolic and diastolic BP were determined to the nearest 2 mmHg by phase I and V of the Korotkoff sounds. Fasting blood samples were collected for the measurements of PG, serum UA, lipid profile, and other biochemical parameters.

### *Measurements*

PG was measured by a glucose oxidase method in a glucose analyzer (model 2300; YSI, Yellow Springs, OH, USA). Total cholesterol (TC), total triglyceride (TG), serum creatinine (Cr), alanine aminotransferase (ALT), and UA levels were measured by using assay kits (Boehringer Mannheim GmbH, Mannheim, Germany) in an automatic blood chemistry analyzer (Model 736; Hitachi, Tokyo, Japan). Serum high-density lipoprotein cholesterol (HDL-C) was determined by an enzymatic cholesterol assay after dextran sulfate precipitation. The reference values for Cr are 0.7–1.5 mg/dL and for ALT 0–40 U/L in men.

### *Statistical analysis*

We divided the participants into 2 groups according to their serum UA levels: those with UA < 7.0 mg/dL and those with UA ≥ 7.0 mg/dL.[13] The metabolic syndrome was defined by the 2005 version of the NCEP ATP III criteria for Asian men.[3,14] The diagnosis of metabolic syndrome was made when participants had 3 or more of the following: fasting PG ≥ 100 mg/dL, TG ≥ 150 mg/dL, HDL-C < 40 mg/dL, BP ≥ 130/85 mmHg, or WC ≥ 90 cm.[3,14] Continuous data were expressed as mean ± SD or median (range). As there was substantial skewing of TG and ALT values, Mann-Whitney *U* tests were applied to the data of TG and ALT for comparison of differences between groups. Two sample *t* tests were applied to other continuous data, and $\chi^2$ tests to categorical data to compare the differences between groups, respectively. Pearson correlation coefficients were used to evaluate correlations between UA and the components of the metabolic syndrome. Logarithmic transformation (Log) of TG values was applied to subordinate the skewness of TG data in the Pearson analysis; this was also followed for Log ALT in the regression analysis. A stepwise multiple logistic regression analysis was performed to examine the relationship between UA and the diagnosis of metabolic syndrome. Participants with or without the metabolic syndrome were dummy-coded and used as dependent variables. UA, BMI, age, Cr, Log ALT, WC, PG, TG, HDL-C, and systolic BP were entered into the regression model as independent variables. A $p$ value of less than 0.05 was considered statistically significant.

Factor analysis using the principal component method with Varimax rotation was performed to examine if UA is clustered with other components of the metabolic syndrome. Variables included in the factor analysis were BMI, WC, PG, Log TG, HDL-C, systolic BP, diastolic BP, and all with eigenvalues greater than 1. Log TG values were used in the analysis for a better fit for models. A factor loading with an absolute value of ± 0.4 or greater was used as cut-off values for data interpretation. The factor analysis was performed again with the above variables and UA to evaluate the contribution of UA to the variance explained in the analysis.

## Results

The clinical characteristics of the study participants are shown in Table 1. We identified more subjects with the metabolic syndrome in participants with hyperuricemia (UA ≥ 7.0 mg/dL) than those with fasting UA < 7.0 mg/dL. The hyperuricemic subjects had larger BMI, wider WC, higher PG and TG, and lower HDL-C levels than their counterparts. There were no significant differences in systolic and diastolic BP between the 2 groups. The hyperuricemic subjects also had higher serum levels of ALT and Cr. Table 2 shows the correlations between serum UA levels and the components of the metabolic syndrome. UA was positively correlated with BMI, WC, PG, Log TG, diastolic BP, and negatively correlated with HDL-C. It was also positively correlated with Log ALT ($r = 0.12$, $p = 0.014$) and serum Cr levels ($r = 0.27$, $p < 0.0001$). The results of the stepwise multiple logistic regression analysis are reported in Table 3. The diagnosis of the metabolic syndrome was significantly associated with ALT and the original components of the syndrome (i.e. WC, PG, TG, HDL-C, and systolic BP). However, we could not demonstrate a significant association between UA and the diagnosis of the metabolic syndrome in the analysis. If we used serum UA ≥ 7.0 mg/dL as a cut-off point for the diagnosis of the metabolic syndrome, the sensitivity would be 58.0% and the specificity would be 55.3%.

Two-factor analysis models were analyzed to explore the contribution of UA as an additional component to the metabolic syndrome. The first model included the

**Table 1.** Descriptive characteristics of study participants by serum uric acid levels

| | UA < 7.0 mg/dL | UA ≥ 7.0 mg/dL | *p** |
|---|---|---|---|
| *n* | 205 | 188 | |
| Age, yr | 51.6 ± 4.3 | 51.5 ± 4.3 | 0.777 |
| BH, cm | 168.7 ± 5.6 | 169.3 ± 5.5 | 0.300 |
| BW, kg | 68.8 ± 8.1 | 73.1 ± 10.1 | < 0.0001 |
| BMI, kg/m$^2$ | 24.2 ± 2.7 | 25.5 ± 3.0 | < 0.0001 |
| WC, cm | 84.6 ± 6.9 | 88.5 ± 7.9 | < 0.0001 |
| UA, mg/dL | 5.9 ± 0.8 | 7.9 ± 0.8 | < 0.0001 |
| PG, mg/dL | 99 ± 9 | 102 ± 9 | 0.002 |
| TG, mg/dL | 111 (732) | 133 (787) | 0.001 |
| Log TG | 2.08 ± 0.23 | 2.13 ± 0.21 | 0.011 |
| TC, mg/dL | 208 ± 38 | 212 ± 39 | 0.316 |
| HDL-C, mg/dL | 49 ± 13 | 47 ± 10 | 0.021 |
| Systolic BP, mmHg | 123 ± 14 | 126 ± 14 | 0.141 |
| Diastolic BP, mmHg | 81 ± 10 | 83 ± 10 | 0.059 |
| ALT, U/L | 23 (123) | 27 (362) | 0.001 |
| Log ALT | 1.39 ± 0.21 | 1.46 ± 0.24 | 0.010 |
| Cr, mg/dL | 1.0 ± 0.1 | 1.1 ± 0.2 | < 0.0001 |
| Metabolic syndrome,† % | 24.9 | 40.4 | 0.001 |

*Data are expressed as mean ± SD or median (range). BH = body height; BW = body weight; BMI = body mass index; WC = waist circumference; UA = uric acid; PG = fasting plasma glucose; TG = fasting total triglyceride; Log TG = logarithmic transformation of TG; TC = fasting total cholesterol; HDL-C = high-density lipoprotein cholesterol; BP = blood pressure; ALT = alanine aminotransferase; Log ALT = logarithmic transformation of ALT; Cr = creatinine.*

**Mann-Whitney U tests were applied to TG and ALT. Two-sample t tests were used to compare other continued data and $\chi^2$ tests to the categorized data for the differences between the 2 groups.*

*†The metabolic syndrome was defined by the 2005 revised version of the National Cholesterol Education Program Adult Treatment Panel III criteria for Asian men.*

**Table 2.** Pearson correlation coefficients of uric acid (mg/dL) with components of the metabolic syndrome and indicated variables in middle-aged Chinese men ($n$ = 393)

| | Pearson | |
|---|---|---|
| | *r* | *p* |
| BMI, kg/m$^2$ | 0.27 | < 0.0001 |
| WC, cm | 0.29 | < 0.0001 |
| PG, mg/dL | 0.21 | < 0.0001 |
| Log TG | 0.24 | < 0.0001 |
| TC, mg/dL | 0.08 | 0.126 |
| HDL-C, mg/dL | –0.23 | < 0.0001 |
| Systolic BP, mmHg | 0.09 | 0.089 |
| Diastolic BP, mmHg | 0.11 | 0.031 |

*BMI = body mass index; WC = waist circumference; PG = fasting plasma glucose; TG = fasting total triglyceride; Log TG = logarithmic transformation of TG; TC = fasting total cholesterol; HDL-C = high-density lipoprotein cholesterol; BP = blood pressure.*

original components of the syndrome without UA (Table 4), and the second model added UA to the variables of interest loaded in the first model (Table 5). In the first model, 2 factors were identified. The first factor, a metabolic factor, included positive loadings for BMI, WC, PG, and Log TG, and negative loading for HDL-C. This factor explained 36.2% of the total variance of our study. Positive loadings for systolic and diastolic BP were identified in the second factor, designated as a BP factor. This factor explained an additional 26.2% of the variance. In model 2, a metabolic factor resembled that of model 1 with the addition of a positive loading of UA to the factor. Systolic and diastolic BP still loaded together as a BP factor. This model explained a slightly smaller proportion of the total variance (56.9%) than model 1 did (62.5%).

**Table 3.** Results of the stepwise logistic regression analysis with the diagnosis of metabolic syndrome* as the dependent variable ($n$ = 393)

| Variables | Exp(B)† | 95% CI | *p* |
|---|---|---|---|
| Log ALT | 7.87 | 1.47–42.21 | 0.016 |
| WC | 1.20 | 1.11–1.29 | < 0.001 |
| PG | 1.13 | 1.08–1.19 | < 0.001 |
| TG | 1.02 | 1.01–1.03 | < 0.001 |
| HDL-C | 0.89 | 0.84–0.94 | < 0.001 |
| Systolic BP | 1.06 | 1.03–1.09 | < 0.001 |

*95% CI = 95% confidence interval; ALT = alanine aminotransferase; Log ALT = logarithmic transformation of ALT; WC = waist circumference; PG = fasting plasma glucose; TG = fasting total triglyceride; Log TG = logarithmic transformation of TG; HDL-C = high-density lipoprotein cholesterol; BP = blood pressure.*

**The metabolic syndrome was defined by the 2005 revised version of the National Cholesterol Education Program Adult Treatment Panel III criteria for Asian men.*

*†The results showed estimates for participants with the metabolic syndrome versus those without it. Variables included in the model were uric acid, body mass index, age, creatinine, ALT, WC, PG, TG, HDL-C, and systolic BP.*

**Table 4.** Results of factor analysis with Varimax rotation: factors and factor loadings without UA

| | Factors | |
|---|---|---|
| | Metabolic | BP |
| BMI | **0.82** * | 0.14 |
| WC | **0.82** | 0.17 |
| PG | **0.53** | 0.13 |
| Log TG | **0.66** | –0.01 |
| HDL-C | **–0.69** | 0.11 |
| Systolic BP | 0.05 | **0.94** |
| Diastolic BP | 0.10 | **0.94** |
| Proportion of variance explained, % | 36.2 | 26.2 |
| Total variance explained, % | 36.2 | 62.5 |

*BMI = body mass index; WC = waist circumference; PG = fasting plasma glucose; TG = fasting total triglyceride; Log TG = logarithmic transformation of TG; HDL-C = high-density lipoprotien cholesterol; BP = blood pressure. *Loading ≥ 0.40 in bold type.*

**Table 5.** Results of factor analysis with Varimax rotation: factors and factor loadings with UA

| | Factors | |
|---|---|---|
| | Metabolic | BP |
| BMI | **0.80** * | 0.14 |
| WC | **0.81** | 0.16 |
| PG | **0.52** | 0.12 |
| Log TG | **0.65** | –0.02 |
| HDL-C | **–0.68** | 0.11 |
| Systolic BP | 0.06 | **0.94** |
| Diastolic BP | 0.10 | **0.94** |
| UA | **0.50** | 0.07 |
| Proportion of variance explained, % | 34.0 | 23.0 |
| Total variance explained, % | 34.0 | 56.9 |

*BMI = body mass index; WC = waist circumference; PG = fasting plasma glucose; TG = fasting total triglyceride; Log TG = logarithmic transformation of TG; HDL-C = high-density lipoprotien cholesterol; BP = blood pressure. *Loading ≥ 0.40 in bold type.*

## Discussion

The diagnosis criteria for the metabolic syndrome proposed by the ATP III have resulted in more discussion of components of the syndrome.[15] Zavaroni et al[7] suggested hyperuricemia to be an additional component of the metabolic syndrome. The American Association of Clinical Endocrinologists once posted hyperuricemia as a major criterion for the metabolic syndrome.[16] Our data show that the contribution of UA as an additional component of the metabolic syndrome seems to be insignificant in middle-aged men.

In the stepwise logistic regression approach, UA levels were not associated with the diagnosis of the syndrome (Table 3). Bonora et al[9] revealed in the Verona Young Men Study that BMI and TG were independent predictors of UA concentrations. Yano and colleagues[17] found that BW was correlated with UA most in more than 6,000 men without using antihypertensive medication. Because UA concentrations could be explained by components of the metabolic syndrome (Table 2), it is possible that there was a lack of association between UA and the diagnosis of the metabolic syndrome. Besides, the sensitivity and specificity of hyperuricemia for the diagnosis of the metabolic syndrome were both below 60% in the study. UA levels seem to be short of predictive power over the diagnosis of the syndrome for these participants.

Factor analysis is a multivariate correlation technique that has been used to understand underlying patterns among variables of the metabolic syndrome.[18] Meigs[18] reviewed a dozen studies using factor analysis to explore the underlying structure of the metabolic syndrome and found that the syndrome was composed of 2–4 domains of phenotypes. An obesity-dyslipidemia-hyperinsulinemia domain is the central feature of the syndrome, and a separate factor for BP is loosely associated with the core feature.[18] Our results accord with the previous reports. We identified 2 domains of phenotypes of the metabolic syndrome by factor analysis in the study: a metabolic factor explained one third of variance, and a BP factor accounted for another 25% of the variance (Table 4). The joint occurrence of the metabolic factor and the BP factor defines a case of the metabolic syndrome. Several earlier analyses have investigated the role of UA in the metabolic syndrome. In a cohort of white males, UA was found to be loaded on a factor also associated with plasma insulin, PG, TG and BMI, but not with BP.[19] In the Miami Community Health Study on 26 nondiabetic men and 24 women, Donahue et al[20] identified a high UA loading on a factor associated with WC, dyslipidemia, insulin resistance, and BP. In a study of nondiabetic Mauritians, Hodge et al[21] suggested that UA was related to a BP factor only in men, but not in women. In our study, UA aggregated with BMI, WC, PG, Log TG, and HDL-C and loaded on the metabolic factor (Table 5). The model loaded with UA explained a slightly smaller proportion of the total variance, as did the model loaded without UA (Tables 4 and 5). The above findings do not suggest a consistent role of UA in the metabolic syndrome across different study populations. The contribution of UA as an additional component of the syndrome to explain the total variance also seems to be insignificant from the results of current factor analysis. We suggested that the information on UA levels might not be an important facet to explore the underlying structure of the metabolic syndrome.

In the study, UA levels were significantly correlated with Log ALT, and ALT activity predicted the diagnosis of the metabolic syndrome (Table 3). Elevated ALT is frequently associated with obesity, dyslipidemia, and insulin resistance[22] and is referred to as nonalcoholic fatty liver disease (NAFLD) if other causes of liver enzyme elevation have been excluded and the subjects have negligible alcohol intake.[23] Marchesini et al[24] suggested that NAFLD could be considered an additional feature of the metabolic syndrome. They also reported that about 30% of NAFLD patients had both elevated UA and ALT levels.[24] Further studies are warranted for a better understanding of the constellation of hyperuricemia and liver enzyme elevation in the metabolic syndrome.

Although the presence of type 2 diabetes does not exclude a diagnosis of the metabolic syndrome,[15] we focus the study on persons without diabetes. A uricosuric effect of glycosuria may exist in patients with diabetes and fasting hyperglycemia, resulting in a reduced serum UA level in overt diabetic patients.[1] In addition, use of antihypertensive agents, especially diuretics, is known to be associated with increased levels of UA. Therefore, the participants in the study were limited to those without diabetes who did not use antihypertensive agents. There were only 10 participants in the study with WC more than 100 cm. In Taiwan, the 75 percentile value of WC for middle-aged men is around 88 cm.[25] Asian men with WC ≥ 90 cm are suggested to have abdominal obesity and to be at risk of comorbidities by the Asian obesity criteria.[14] WC ≥ 90 cm was used in this study for the diagnosis of the metabolic syndrome by the recently revised ATP III recommendations.[3]

In conclusion, the contribution of UA as an additional component of the metabolic syndrome seems to be insignificant to the results of factor analysis. We propose that hyperuricemia might not be an important facet for the understanding of the underlying structure of the metabolic syndrome.

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