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CLINICAL RESEARCH STUDY

Prevalence of the Metabolic Syndrome in Individuals with Hyperuricemia

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ABSTRACT

PURPOSE: The link between hyperuricemia and insulin resistance has been noted, but the prevalence of the metabolic syndrome by recent definitions among individuals with hyperuricemia remains unclear. Our objective was to determine the prevalence of the metabolic syndrome according to serum uric acid levels in a nationally representative sample of US adults.

METHODS: By using data from 8669 participants aged 20 years and more in The Third National Health and Nutrition Examination Survey (1988-1994), we determined the prevalence of the metabolic syndrome at different serum uric acid levels. We used both the revised and original National Cholesterol Education Program Adult Treatment Panel (NCEP/ATP) III criteria to define the metabolic syndrome.

RESULTS: The prevalences of the metabolic syndrome according to the revised NCEP/ATP III criteria were 18.9% (95% confidence interval [CI], 16.8-21.0) for uric acid levels less than 6 mg/dL, 36.0% (95% CI, 32.5-39.6) for uric acid levels from 6 to 6.9 mg/dL, 40.8% (95% CI, 35.3-46.4) for uric acid levels from 7 to 7.9 mg/dL, 59.7% (95% CI, 53.0-66.4) for uric acid levels from 8 to 8.9 mg/dL, 62.0% (95% CI, 53.0-66.4) for uric acid levels from 9 to 9.9 mg/dL, and 70.7% for uric acid levels of 10 mg/dL or greater. The increasing trends persisted in subgroups stratified by sex, age group, alcohol intake, body mass index, hypertension, and diabetes. For example, among individuals with normal body mass index (<25 kg/m^2), the prevalence increased from 5.9% (95% CI, 4.8-7.0), for a uric acid level of less than 6 mg/dL, to 59.0%, (95% CI, 20.1-97.9) for a uric acid level of 10 mg/dL or greater. With the original NCEP/ATP criteria, the corresponding prevalences were slightly lower.

CONCLUSIONS: These findings from a nationally representative sample of US adults indicate that the prevalence of the metabolic syndrome increases substantially with increasing levels of serum uric acid. Physicians should recognize the metabolic syndrome as a frequent comorbidity of hyperuricemia and treat it to prevent serious complications.

KEYWORDS: Hypertension; Insulin resistance; Metabolic syndrome; NHANES III; Obesity; Uric acid

The metabolic syndrome, which consists of multiple interrelated conditions, increases the risk for atherosclerotic cardiovascular disease and type 2 diabetes,[1-4] as well as mortality from cardiovascular disease and all causes.[5-9] The syndrome affects more than 50 million Americans.[2,8]

A number of studies reported significant associations between serum uric acid levels and individual components of the metabolic syndrome,[10-14] but the scope of prevalence of the metabolic syndrome using recent definitions among individuals with hyperuricemia is unknown. Renal clearance of urate is inversely related to the degree of insulin resistance.[15] Thus, the reduced renal excretion of urate among patients with the metabolic syndrome may explain the increased frequency of hyperuricemia. On the basis of these data, hyperuricemia has been suggested as a simple marker of the metabolic syndrome.[12,13,16] However, without

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clear knowledge about the prevalence of the syndrome among individuals with hyperuricemia, the potential utility of the marker remains unclear. Furthermore, if the prevalence varies substantially depending on the degree of hyperuricemia, the information should be reflected in an index of clinical suspicion for the co-presence of the metabolic syndrome.

To address these issues, we determined the prevalence of the metabolic syndrome among individuals with different serum uric acid levels as determined by the Third National Health and Nutrition Examination Survey (NHANES III).

CLINICAL SIGNIFICANCE

- The prevalence of the metabolic syndrome increases substantially with increasing levels of hyperuricemia.
- The symptoms of metabolic syndrome increase with increasing levels of hyperuricemia, including abdominal obesity, hypertriglyceridemia, low HDL cholesterol, high blood pressure, and high fasting glucose.
- Physicians should recognize the metabolic syndrome as a frequent comorbidity of hyperuricemia and treat it to prevent serious complications.

METHODS

Study Population

Conducted between 1988 and 1994, the NHANES III included a representative sample of the noninstitutionalized US civilian population, which was selected using a multistage, stratified sampling design. Persons 60 years and older and African American and Mexican American persons were oversampled. In the current study, we analyzed data for 8669 men and nonpregnant women aged at least 20 years who attended the medical examination, had fasted at least 8 hours before the blood collection, and had complete information to allow definition of the metabolic syndrome[8] and measurement of serum uric acid levels.

Assessment of the Metabolic Syndrome

We used both the revised and original National Cholesterol Education Program Adult Treatment Panel (NCEP/ATP) III criteria to define the metabolic syndrome. According to the original NCEP/ATP III criteria,[8,17] participants with 3 or more of the following criteria were defined as having the metabolic syndrome: abdominal obesity (waist circumference $>$102 cm in men and $>$88 cm in women); hypertriglyceridemia ($\geq$150 mg/dL [1.70 mmol/L]); low high-density lipoprotein (HDL) cholesterol ($<$40 mg/dL [1.04 mmol/L] in men and $<$50 mg/dL [1.30 mmol/L] in women); high blood pressure ($\geq$130/85 mm Hg); and high fasting glucose ($\geq$110 mg/dL [$\geq$6.1 mmol/L]). We counted participants who reported currently using antihypertensive or antidiabetic medication (insulin or oral agents) as participants with high blood pressure or diabetes, respectively.[8] Because the original NCEP/ATP III criteria were recently revised to require a lower fasting glucose level (ie, $\geq$100 mg/dL [$\geq$5.6 mmol/L]),[1,18] we report our results using the original criteria, as well as those using the revised criteria in this study. Serum triglycerides were measured enzymatically after hydrolyzation to glycerol (Hitachi 704 Analyzer; Hitachi, Tokyo, Japan). HDL cholesterol was measured after the precipitation of other lipoproteins with a heparin-manganese chloride mixture (Hitachi 704 Analyzer).[19] Serum glucose concentration was measured using an enzymatic reaction (Cobas Mira assay; Roche, Basel, Switzerland). Details about the laboratory procedures of all these tests are published elsewhere.[19] Three blood pressure readings were obtained in the mobile examination center. The average of the second and third systolic and diastolic blood pressure readings was used in the analyses.

Uric Acid Measurement

Serum uric acid was measured by oxidization with the specific enzyme uricase to form allantoin and H_2O_2 (Hitachi Model 737 Multichannel Analyzer, Boehringer Mannheim Diagnostics, Indianapolis, Ind) as detailed elsewhere.[19] Values are reported in milligrams per deciliter; to convert to micromoles per liter, multiply by 59.48.

Statistical Analysis

All statistical analyses were performed using survey commands of STATA (ie, SVY) to incorporate sample weights and adjust for clusters and strata of the complex sample design (Version 9, STATA Corporation, College Station, Tex). The prevalence of the metabolic syndrome (%) among the total study population was calculated according to 6 categories of serum uric acid levels: less than 6 mg/dL, 6 to 6.9 mg/dL, 7 to 7.9 mg/dL, 8 to 8.9 mg/dL, 9 to 9.9 mg/dL, and 10 mg/dL or more. We performed a logistic regression to evaluate the association between uric acid categories of 6 mg/dL or greater and the metabolic syndrome compared with the lowest uric acid level category ($<$6 mg/dL) and calculated unadjusted odds ratios (OR), and age- and sex-adjusted OR. We calculated multivariate OR after adjusting for age, sex, race/ethnicity, smoking status (current, former, or never), body mass index (BMI) (6 categories), physical activity (5 categories), alcohol consumption (drinks per month), diabetes (by self-report of a physician diagnosis or fasting glucose $\geq$ 126 mg/dL [$\geq$6.99 mmol/L]), total energy intake (continuous), glycemic load (quintiles), calcium intake (quintiles), magnesium intake (quintiles), and cereal fiber intake (quintiles). These covariate data were based on corresponding questionnaires of the NHANES III, including a food frequency questionnaire, single 24-hour dietary recall, and physical activity data.[19,20-22] Trends across categories of serum uric acid levels were assessed in logistic regression models by using the median values of each category.

Table 1 Prevalence of the Metabolic Syndrome According to Serum Uric Acid Levels*

	Uric Acid Levels (mg/dL)					
	<6	6-6.9	7-7.9	8-8.9	9-9.9	≥10
Revised NCEP/ATP III						
Prevalence, % (95% CI)	18.9 (16.8-21.0)	36.0 (32.5-39.6)	40.8 (35.3-46.4)	59.7 (53.0-66.4)	62.0 (41.1-83.0)	70.7 (51.4-89.9)
Unadjusted OR (95% CI)	1.0	2.42 (2.03-2.88)	2.96 (2.31-3.80)	6.36 (4.80-8.43)	7.02 (2.86-17.25)	10.34 (4.10-26.05)
Age- and sex-adjusted OR (95% CI)	1.0	2.91 (2.32-3.66)	3.60 (2.68-4.85)	7.49 (5.36-10.45)	8.98 (3.43-23.55)	6.25 (2.22-17.58)
Multivariate OR†(95% CI)	1.0	2.29 (1.85-2.83)	2.49 (1.79-3.49)	5.23 (3.82-7.17)	5.71 (2.51-12.96)	6.50 (1.85-22.76)
Original NCEP/ATP III						
Prevalence, % (95% CI)	15.6 (13.7-17.4)	30.5 (27.0-34.0)	32.7 (27.5-37.8)	53.8 (45.8-61.7)	48.7 (31.1-66.2)	66.6 (48.0-85.2)
Unadjusted OR (95% CI)	1.0	2.38 (1.95-2.90)	2.63 (2.02-3.41)	6.31 (4.59-8.66)	5.14 (2.45-10.77)	10.81 (4.65-25.15)
Age- and sex-adjusted OR (95% CI)	1.0	2.98 (2.34-3.79)	3.28 (2.38-4.53)	7.85 (5.43-11.33)	6.59 (2.80-15.51)	7.27 (2.89-18.25)
Multivariate OR† (95% CI)	1.0	2.26 (1.80-2.85)	2.13 (1.50-3.02)	5.57 (3.80-8.17)	4.00 (1.44-11.1)	7.95 (2.36-26.8)

OR = odds ratio; CI = confidence interval; NCEP/ATP = National Cholesterol Education Program Adult Treatment Panel.

*Data are presented incorporating sample weights and adjusted for clusters and strata of the complex sample design of NHANES III.

†Adjusted for age, sex, race/ethnicity, smoking status (current, former, or never), BMI (6 categories), physical activity (5 categories), alcohol consumption (drinks per month), diabetes (by self-report of a physician diagnosis or fasting glucose ≥126 mg/dL [≥6.99 mmol/L]), total energy intake (continuous), glycemic load (quintiles), calcium intake (quintiles), magnesium intake (quintiles), and cereal fiber intake (quintiles).

We also calculated prevalences by demographic factors (sex and age group) and by major associated factors of hyperuricemia, including BMI (<25 vs ≥ 25 kg/m^2); alcohol intake (use or no use); hypertension (high blood pressure as defined above or antihypertensive medication use); and diabetes (by self-report of a physician diagnosis or fasting glucose ≥ 126 mg/dL [≥6.99 mmol/L]). For these subgroup analyses, we grouped uric acid levels in 4 categories: less than 6 mg/dL, 6 to 7.9 mg/dL, 8 to 9.9 mg/dL, and 10 mg/dL or more. For all measures, we calculated 95% confidence intervals (CIs). All *P* values are 2-sided.

RESULTS

The mean age of the study sample was 44 years, 50% were male, 76% were white, and the mean BMI was 26.5 kg/m^2. The mean uric acid level was 5.42 mg/dL (95% CI, 5.37-5.46 mg/dL). There was a graded increase in the prevalence of the metabolic syndrome according to the revised NCEP/ATP III criteria among individuals with increasing levels of serum uric acid, up to 70% (95% CI, 51.4-89.9) among individuals with serum uric acid level of 10 mg/dL or greater (Table 1). Similarly, the increasing trend was evident with the original NCEP/ATP criteria, although the corresponding prevalences were slightly lower. There were increasing trends of ORs for the association between increasing levels of serum uric acid and the metabolic syndrome (*P* values for trend in unadjusted, age- and-sex adjusted, and multivariate analyses < .001) (Table 1). Similarly, the prevalence of individual metabolic abnormalities increased with increasing levels of serum uric acid, except for a slight decrease in the prevalence of abdominal obesity in the highest category of uric acid level (Table 2).

The increasing trends with increasing uric acid levels persisted in both sexes, but the prevalence of the metabolic syndrome among women tended to be higher than among men at a given category of uric acid levels of 6 mg/dL or more (Figure 1). The general increasing trends with increasing uric acid levels tended to persist among different age groups (Figure 2), but precision of the weighted prevalence estimates, particularly in the highest uric acid category, seemed unstable with the smaller subgroup sizes.

We also stratified the prevalence of the metabolic syndrome by major associated factors of hyperuricemia (ie, BMI, alcohol use, hypertension, and diabetes) (Table 3). As expected, the prevalence of the metabolic syndrome was higher when these stratified factors were present. However, all stratified prevalences substantially and significantly in-

Table 2 Prevalence of Individual Metabolic Abnormalities of the Metabolic Syndrome According to Serum Uric Acid Levels*

Uric Acid Levels (mg/dL)	<6	6-7.9	8-9.9	≥10
Abdominal obesity	32.1 (30.1-34.2)	41.5 (38.7-44.2)	57.7 (51.1-64.4)	49.2 (28.4-70.0)
Hypertriglyceridemia	20.2 (17.7-22.7)	42.9 (39.6-46.2)	55.9 (47.0-64.9)	64.7 (45.5-83.8)
Low HDL cholesterol	33.1 (30.6-35.6)	43.3 (39.0-47.7)	51.4 (44.2-58.7)	59.4 (41.1-77.8)
High blood pressure or medication use	24.5 (22.7-26.3)	41.3 (38.0-44.6)	60.7 (52.8-68.5)	84.7 (70.7-98.6)
Fasting glucose ≥110 mg/dL or medication use	8.6 (7.5-9.6)	16.0 (14.2-17.8)	20.1 (14.2-26.0)	35.6 (15.0-56.2)
Fasting glucose ≥100 mg/dL or medication use	22.6 (20.4-24.9)	36.6 (34.3-39.0)	39.4 (30.7-48.1)	53.8 (32.4-75.3)

HDL = high-density lipoprotein.

*Data are presented incorporating sample weights and adjusted for clusters and strata of the complex sample design of NHANES III.

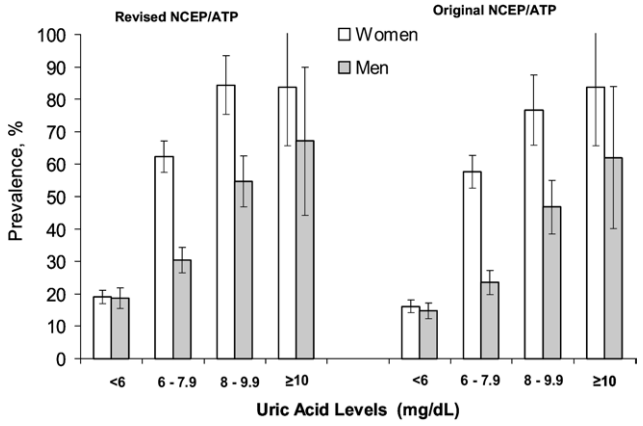

Figure 1 Prevalence of the metabolic syndrome according to serum uric acid levels stratified by sex. Error bars indicate 95% CIs. Data are presented incorporating sample weights and adjusted for clusters and strata of the complex sample design of NHANES III. NCEP/ATP = National Cholesterol Education Program Adult Treatment Panel.

creased with increasing levels of serum uric acid. For example, even among individuals with normal BMI (<25 kg/m^2), the prevalence increased from 5.9% (95% CI, 4.8-7.0), for a uric acid level less than 6 mg/dL, to 59.0%, (20.1-97.9) for a uric acid level of 10 mg/dL or more (Table 3).

DISCUSSION

In this nationally representative sample of men and women, we found that there was a graded increase in the prevalence of the metabolic syndrome among individuals with increasing levels of hyperuricemia, up to 70% among individuals with the highest serum uric acid levels (≥10 mg/dL). This prevalence was approximately 4 times that among adults with the lowest serum uric acid levels (<6 mg/dL). The increasing prevalence of individual metabolic abnormalities with increasing levels of hyperuricemia was appar-

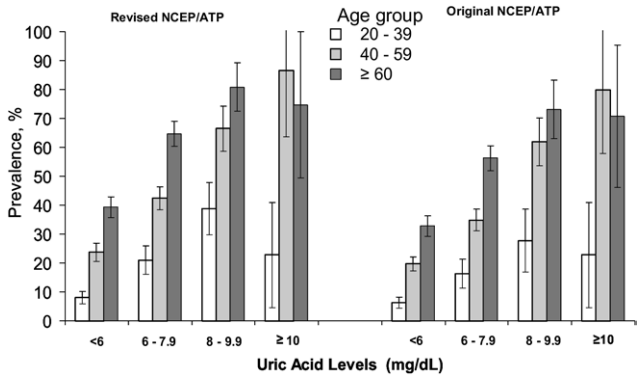

Figure 2 Prevalence of the metabolic syndrome according to serum uric acid levels stratified by age group. Error bars indicate 95% CIs. Data are presented incorporating sample weights and adjusted for clusters and strata of the complex sample design of NHANES III. NCEP/ATP = National Cholesterol Education Program Adult Treatment Panel.

Table 3 Prevalence of the Metabolic Syndrome According to Serum Uric Acid Levels, Stratified by Major Associated Factors of Hyperuricemia*

	Revised NCEP/ATP Definition				Original NCEP/ATP III Definition			
Uric Acid Levels (mg/dL)	<6	6-7.9	8-9.9	≥10	<6	6-7.9	8-9.9	≥10
BMI, kg/m^2								
<25 (n = 3464)	5.9 (4.8-7.0)	13.5 (9.7-17.3)	26.0 (11.5-40.4)	59.0 (20.1-97.9)	4.0 (3.0-4.9)	9.2 (6.0-12.5)	23.3 (8.0-38.6)	59.0 (20.1-97.9)
≥25 (n = 5205)	34.1 (30.4-37.8)	48.6 (44.7-52.5)	66.0 (58.8-73.3)	75.5 (51.9-99.1)	29.1 (25.9-32.4)	41.2 (37.4-45.0)	57.3 (49.4-65.2)	69.8 (47.0-92.6)
Alcohol use								
No (n = 4352)	13.9 (11.5-16.3)	28.8 (25.4-32.3)	58.3 (47.0-69.6)	57.0 (26.9-87.0)	11.0 (9.1-12.9)	21.6 (18.7-24.5)	48.5 (37.6-59.4)	49.9 (21.2-78.6)
Yes (n = 4317)	25.0 (22.7-27.3)	50.6 (44.6-56.6)	63.2 (47.3-79.1)	88.9 (79.0-98.8)	21.2 (18.8-23.6)	45.4 (39.2-51.7)	58.2 (42.9-73.5)	88.9 (79.0-98.8)
Hypertension†								
No (n = 5335)	8.7 (7.3-10.1)	18.7 (16.0-21.3)	35.1 (20.5-49.7)	37.5 (00.0-79.1)	6.6 (5.3-7.8)	13.6 (10.6-16.6)	24.2 (12.0-36.3)	25.0 (00.0-60.0)
Yes (n = 3334)	50.2 (46.0-54.4)	64.5 (59.6-69.5)	76.7 (68.2-85.1)	76.7 (56.3-97.0)	43.3 (39.0-47.6)	56.2 (51.8-60.6)	70.8 (61.7-79.9)	74.2 (54.2-94.1)
Diabetes‡								
No (n = 809)	15.6 (13.9-17.4)	33.4 (30.5-36.2)	57.0 (49.8-64.1)	66.6 (44.4-88.7)	12.3 (10.8-13.8)	26.5 (23.5-29.5)	48.5 (41.5-55.6)	62.0 (40.5-83.4)
Yes (n = 7860)	76.8 (70.0-83.7)	87.4 (81.6-93.2)	97.2 (93.5-100.)	100	74.7 (67.1-82.4)	86.7 (80.7-92.8)	96.0 (91.3-100)	100

NCEP/ATP = National Cholesterol Education Program Adult Treatment Panel; BMI = body mass index.
*Data are presented incorporating sample weights and adjusted for clusters and strata of the complex sample design of NHANES III.
†High blood pressure or antihypertensive medication use (see "Methods" for details).
‡Self-reported physician diagnosis of diabetes or fasting glucose ≥ 126 mg/dL (≥6.99 mmol/L).

ent, and the graded increase persisted across the different subgroups stratified by age, sex, alcohol use, BMI, hypertension, and diabetes. Although the association between hyperuricemia and insulin resistance has been reported, this is the first population-based study to quantify the prevalence of the metabolic syndrome at different levels of hyperuricemia.

There are several important implications of our results. The prevalence estimates determined in the current study provide the probabilities of concomitant presence of the metabolic syndrome among individuals with differing degrees of hyperuricemia. The presence of hyperuricemia, particularly at higher levels, should trigger a high level of clinical suspicion and investigation for a potential coexistence of the metabolic syndrome. If present, the syndrome needs to be recognized as a potentially more life-threatening factor than hyperuricemia,[12] given the serious associated complications.[1,2,7,8] The cornerstones of treatment for the syndrome are managing weight and ensuring appropriate levels of physical activity.[8] Recent studies demonstrated that lifestyle interventions or medications may delay or prevent the transition from impaired glucose tolerance to type 2 diabetes mellitus and provide relevant treatment paradigms for patients with the metabolic syndrome.[23-25]

Long-term dietary recommendations for the majority of individuals with hyperuricemia or gout should take this frequent comorbidity into account. For example, conventional dietary recommendations for hyperuricemia or gout have focused on restriction of purine intake, although low-purine diets are often high in carbohydrate and saturated fat.[13] These macronutrients are associated with an increased risk of the insulin resistance syndrome and associated major consequences.[26-28] Furthermore, these macronutrients tend to lead to higher serum insulin levels, which are known to reduce renal excretion of urate,[15,27,29,30] thus potentially further increasing the serum uric acid level. Given the frequent association between hyperuricemia and the metabolic syndrome, it is imperative to develop appropriate dietary and other lifestyle guidelines taking into account improving hyperuricemia and overall long-term health effects. In addition, the growing epidemics of obesity[31,32] and the metabolic syndrome[33] present a substantial challenge in the prevention and management of gout with hyperuricemia.[14] Because these conditions would likely also share important parts of public health and clinical management approaches, future studies may need to focus on developing the overall optimal strategies for improving these concurrent conditions.

Our results expand on previous studies that showed a close relation between hyperuricemia and the insulin resistance syndrome,[10-12] recent case series of gout and the metabolic syndrome,[34,35] and our recent report about a high prevalence of the metabolic syndrome among those with gout,[36] thereby supporting a pathogenetic overlap between these conditions. Higher insulin levels are known to reduce renal excretion of urate.[15,27,29,30] For example, exogenous insulin can reduce the renal excretion of urate in both healthy and hypertensive subjects.[12,29,30] Insulin may enhance renal urate reabsorption by stimulation of urate-anion exchanger URAT1[37] and/or the Na^+-dependent anion cotransporter in brush border membranes of the renal proximal tubule.[14] In addition, because serum levels of leptin and urate tend to increase together,[38,39] some investigators have suggested the leptin may affect renal reabsorption.[14] Finally, in the insulin resistance syndrome, impaired oxidative phosphorylation may increase systemic adenosine concentrations by increasing the intracellular levels of coenzyme A esters of long-chain fatty acids.[14] Increased adenosine, in turn, can result in renal retention of sodium, urate, and water.[40-43] Some have speculated that chronically increased extracellular adenosine concentrations may also contribute to hyperuricemia by increasing urate production.[40]

The strengths and limitations of our study deserve comment. This study was performed in a nationally representative sample of US women and men; thus, the findings are likely to be generalizable to US men and women. The current study provides national estimates of the prevalence of the metabolic syndrome among individuals with different levels of serum uric acid, a finding that the NHANES cross-sectional study design was well suited to address. However, the current cross-sectional design is not able to address potential temporal relations between hyperuricemia and the metabolic syndrome, which need to be evaluated by longitudinal studies. The 2 variables related in our study were ascertained objectively without reliance on study participants' recall. Thus, recall bias, another generally recognized weakness of a cross-sectional design, is not applicable in this setting.

CONCLUSION

These findings from a nationally representative sample of US adults indicate that the prevalence of the metabolic syndrome increases substantially with increasing serum uric acid levels. These prevalence estimates should be reflected in an index of clinical suspicion for the concomitant presence of the metabolic syndrome. Physicians should recognize the metabolic syndrome as a frequent comorbidity of hyperuricemia and treat it to prevent serious complications.

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