

# UNDERWRITER RESOURCE

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## Serum Uric Acid Wolf in Sheep's Clothing: The New Face of an Old Test

Uric acid (UA) is the final breakdown product of unwanted purine nucleotides which are the principle constituents of cellular energy stores such as adenosine triphosphate (ATP), components of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Elevated serum UA level (hyperuricemia) is a well known cause of gout, kidney stones and a rare cause of uric acid nephropathy. Recent medical literature suggests an association between hyperuricemia and incidence of hypertension,

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metabolic syndrome, diabetes, cardiovascular disease (CVD) and increased CVD mortality. The ensuing discussion will review the evidence for this assertion and consider the appropriate use of serum uric acid (SUA) measurement in risk selection for life insurance.

Hyperuricemia is usually diagnosed when SUA levels are greater than 7 mg/dl (>420  $\mu\text{mol/L}$ ) in men and greater than 6 mg/dl (>300  $\mu\text{mol/L}$ ) in women. It is estimated that five to ten percent of adult Americans have hyperuricemia. The blood level of urate is maintained by the balance between dietary intake, production and excretion. Dietary sources, mainly meat and seafood, account for 90 percent of the SUA elevation. As approximately two thirds of the daily turnover of urate is excreted by the kidneys, renal insufficiency is a frequent cause of hyperuricemia. Alcohol, another cause of hyperuricemia, elevates the SUA level by increasing its production and reducing its excretion by the kidneys. Diuretics, such as thiazides, increase SUA by stimulating both sodium and urate reabsorption in the proximal tubule of the kidney. Rare causes of hyperuricemia include hematological malignancies and psoriasis.

## Incidence of Hypertension

The positive association between hyperuricemia and hypertension was observed over a century ago. Several cross-sectional studies have consistently noted that more than a quarter of patients with untreated hypertension have elevated SUA levels. Considerable experimental evidence supports a causal role for UA in the development of hypertension. Mild hyperuricemia in rats leads to elevated blood pressure (BP), which can be prevented by treatment that lowers the SUA level. Clinical data also corroborate a possible causative role for UA in systemic hypertension.

The Bogalusa Heart Study (Hypertension. 2005; 45:34-38.) examined 334 whites and 243 blacks enrolled as children age 5 to 17 and as adults age 18 to 35. The average follow-up period was 12 years. Childhood SUA was significantly correlated with childhood and adult systolic and diastolic BP. Change in SUA level was a significant predictor of adult diastolic BP but not adult systolic BP in a multivariate regression analysis adjusting for age, sex, race, childhood body mass index and childhood SUA level. According to this study, elevated childhood SUA level is associated with increased BP beginning in childhood and higher BP that persists into adulthood, in males and females, whites and blacks, suggesting that early elevation in SUA level may play a key role in the development of human hypertension.

The Framingham Study ((Hypertension. 2005; 45:28-33) explored the relationship of SUA to hypertension incidence and BP progression. In this study of 3,329 participants (mean age 48.7; 55.6% women) free of hypertension, myocardial infarction, heart failure, renal failure or gout, SUA was measured at baseline. The mean SUA level for this group was 4.9 mg/dl and the standard deviation was 1.3 mg/dl. At follow-up four years from baseline, 458 persons (13.8%) had developed hypertension and 1,201 persons (36.1%) had experienced progression to a higher BP stage (JNC VI stage – January 2008 issue of Underwriter

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**Table 1. SUA Level at Baseline and Risk of BP Outcomes at 4 Years**

	Per Standard Deviation Increase in SUA Level		
	Unadjusted	Age & Sex Adjusted	Multivariable*
<b>Odds Ratio for Developing Hypertension</b>	1.29 (1.17–1.42)	1.26 (1.12–1.41)	1.17 (1.02–1.33)
<b>Odds Ratio for Increase in BP by One or More Stage</b>	1.15 (1.07–1.23)	1.14 (1.04–1.24)	1.11 (1.01–1.23)

\*Models adjusted for age, sex, BMI, diabetes, interim weight change, smoking, alcohol intake, serum creatinine, glomerular filtration rate, proteinuria and baseline systolic and diastolic BP and BP category. Baseline use of cardiac medication for indications other than hypertension was also considered.

Source: Hypertension. 2005; 45:28-33.

**Table 2. NCEP/ATP III Criteria for Metabolic Syndrome**

Risk Factor	Defining Level
<b>Abdominal Obesity (Waist Circumference)</b>	
Men	>40 inches
Women	>35 inches
Triglycerides	≥150 mg/dl
<b>HDL Cholesterol</b>	
Men	<40mg/dl
Women	<50 mg/dl
Blood Pressure	Systolic ≥130 mmHg Diastolic ≥85 mmHG
Fasting Glucose	≥110 mg/dl

Source: NIH Publication No. 01-3670.

**Table 3. Odds Ratio for Metabolic Syndrome by Quartiles of Uric Acid**

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Uric Acid in mg/dl	0.8–3.9	4.0–4.6	4.7–5.3	5.4–8.9
Men (95% CI)	1.0	0.92 (0.74 to 1.14)	1.52 (1.25 to 1.65)	1.97 (1.61 to 2.40)
Women (95% CI)	1.0	1.06 (0.60 to 1.87)	2.18 (1.30 to 3.64)	4.17 (2.56 to 6.79)

Source: Arteriosclerosis, Thrombosis, and Vascular Biology. 2005; 25:1038

Resource). In this community-based sample, SUA level was an independent predictor of hypertension incidence and longitudinal BP progression (table 1) during a four-year follow-up.

This increased incidence of hypertension was confirmed by investigators in another study, using data from the Multiple Risk Factor Intervention Trial (Hypertension. 2007; 49:298-303.). They concluded that hyperuricemia increased the risk of developing hypertension by approximately 80 percent, during a six year period, independent of baseline BP measurements, renal function, serum lipids, BMI, proteinuria, alcohol usage and age.

**Metabolic Syndrome**

The clinical features of metabolic syndrome are listed in table 2. Based on National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) criteria, a diagnosis of metabolic syndrome is made when three or more criteria are present. According to the National Health and Nutrition Examination Survey (NHANES) 1999–2000 data, the age adjusted prevalence of metabolic syndrome fitting these criteria was 27 percent (Diabetes Care 2004; 27:2444–2449). It is well known that those diagnosed with metabolic syndrome are at increased risk of developing diabetes and CVD.

One feature that is common to all patients with metabolic syndrome is an elevated SUA level. Although this was considered to be secondary to hyperinsulinemia, recent evidence supports a primary role for uric acid in mediating this syndrome. Specifically, fructose, which rapidly can cause metabolic syndrome in rats, also raises UA level, and lowering UA level in fructose-fed rats prevents features of the metabolic syndrome (J Am Soc Nephrol. 17: S165–S168, 2006.).

Investigators from Tokyo, Japan, studying the association between SUA and metabolic syndrome (Arteriosclerosis, Thrombosis, and Vascular Biology. 2005; 25:1038), analyzed cross-sectional data from 8,144 individuals who underwent general health screening. They discovered that the prevalence of metabolic syndrome showed a graded increase according to SUA values in both genders. After adjusting for age, total cholesterol and smoking status, the odds ratios for metabolic syndrome by sex-specific quartiles were 1.0, 0.92, 1.52 and 1.97 in men and 1.0, 1.06, 2.18 and 4.17 in women (table 3).

Another study (Arthritis & Rheumatism 2007; 57:109–115), using data from Third NHANES 1988–1994, determined the prevalence of metabolic syndrome among individuals with gout and quantified the magnitude of the association between the two conditions.

In this study, the prevalence of metabolic syndrome according to NCEP/ATP III criteria was 62.8 percent among individuals with gout and 25.4 percent among individuals without gout. The unadjusted and age- and sex-adjusted odds ratios of metabolic syndrome for individuals with gout were 4.96 and 3.05, respectively. These findings indicate that the prevalence of metabolic syndrome is remarkably high among individuals with gout compared to those without gout. Further, this study by implication, confirms the presence of a relationship between hyperuricemia and increased incidence of metabolic syndrome discovered by the investigators from Japan.

**Incidence of Type-2 Diabetes**

SUA level is positively associated with serum glucose in healthy subjects. However, in diabetics with hyperglycemia, the SUA level is apparently low. Since SUA is a risk factor for metabolic syndrome, it is highly likely that it also would be a risk factor for type-2 diabetes. The Rotterdam Study (Diabetes Care. 2008; 31:361-62) confirms this relationship.

The Rotterdam Study is a population-based prospective cohort study of 4,536 subjects, age 55 and older, free from diabetes at baseline. The study subjects were followed for a mean of 10.1 years. During this period, diabetes developed in 462 subjects.

Based on the analysis of the collected data, the investigators concluded, the age and sex-adjusted hazard ratios (HR) for developing diabetes were 1.30 for the second, 1.63 for the third and 2.83 for the fourth quartile of SUA, in comparison with the first quartile. After adjustment for BMI, waist circumference, systolic and diastolic blood pressure and HDL cholesterol, the HR decreased to 1.08, 1.12, and 1.68 respectively. The results of this population-based study suggest that elevated SUA level is a strong and independent risk factor for diabetes (table 4).

### Cardiovascular Mortality

The association of serum uric acid with CVD has been acknowledged for nearly half a century. During this time many clinical and epidemiological research studies have convincingly demonstrated a positive association of SUA level with all cardiovascular events and mortality.

For instance, a cross-sectional population-based NHANES extended follow-up study (JAMA 2000; 283:2404-2410) of 5,926 subjects age 25 to 74 had SUA level measured at baseline; the subjects were followed for an average of 16.4 years. The mean age of the study population was 48.1, the mean SUA level was 5.5 mg/dl and the standard deviation was 1.4 mg/dl.

Among the 5,926 subjects, there were a total of 1,593 deaths (26.9%) in the study group. Of the total deaths, 731 (45.9%) were attributed to CVD (coronary artery disease, 421; stroke, 111; and other cardiovascular deaths, 199), and 429 deaths (26.9%) were cancer related. In this study, the SUA level had a positive relationship to cardiovascular mortality in men and women and white persons and black persons. Cox regression analysis showed that for each 1.0 mg/dl increase in uric acid level, HR for CVD mortality and CAD mortality were 1.09 and 1.17 for men and 1.26 and 1.30 for women, respectively (table 5). The impact of uric acid on mortality was independent of age, race, body mass index, smoking status, alcohol consumption, cholesterol level, history of hypertension and diabetes, and diuretic use.

This association between SUA and cardiovascular mortality was confirmed by another population-based prospective cohort study (Arch Intern Med. 2004; 164:1546-1551) of 1,423 middle-aged Finnish men who were initially without cardiovascular disease, cancer or diabetes. The investigators found that SUA level is a strong predictor of CVD mortality in healthy middle-aged men, independent of variables commonly associated with gout or the metabolic syndrome.

In this study, there were 157 deaths during a mean follow-up of 11.9 years. Of these, 55 were due to cardiovascular disease. The investigators found that those with SUA level in the upper third were associated with a greater than 2.5-fold higher risk of death from CVD than those with SUA level in the lower third. This association strengthened after adjustment for age and risk factors associated with gout and metabolic syndrome (table 6).

### Uric Acid in Risk Selection

Hyperuricemia has traditionally been utilized in underwriting as a marker of excessive alcohol use. It is evident from the information presented that it is much more than that and that hyperuricemia is an indicator of a propensity for many diseases such as hypertension, diabetes, coronary artery disease and stroke. It is also a marker for increased cardiovascular mortality.

**Table 4. HR for Diabetes by Quartiles of SUA**

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Uric Acid in mg/dl	0.8–3.9	4.0–4.6	4.7–5.3	5.4–8.9
HR, age and sex adjusted (95% CI)	1.0	0.92 (0.74 to 1.14)	1.52 (1.25 to 1.65)	1.97 (1.61 to 2.40)
HR with additional adjustments* (95% CI)	1.0	1.06 (0.60 to 1.87)	2.18 (1.30 to 3.64)	4.17 (2.56 to 6.79)

\*Age and sex adjusted + adjustment for BMI, waist circumference, systolic and diastolic blood pressure, and HDL cholesterol

**Table 5. HR\* for CVD & CAD Mortality for 1mg/dl Increase in SUA Level**

	CVD	CAD
Men (95% CI)	1.09 (1.02-1.18)	1.17 (1.06-1.28)
Women (95% CI)	1.26 (1.16-1.36)	1.30 (1.17-1.45)

\*after adjustment for age, race, body mass index, smoking status, alcohol consumption, cholesterol level, history of hypertension and diabetes, and diuretic use

**Table 6. Risk of Death for SUA Level Tertiles after Adjustment for Risk Factors**

	Tertile 1 (Reference)	Tertile 2	Tertile 3
Uric acid level in mg/dL	3.03-5.04	5.05-5.88	5.89-9.58
Risk of death from CVD	1	4.98 (1.61-15.4)	4.77 (1.50 to 15.1)
Risk of death from any cause (95% confidence level)	1	1.74 (1.05-2.88)	1.85 (08-3.17)

Source: (Arch Intern Med. 2004; 164:1546-1551)

Even though hyperuricemia is usually associated with the other cardiovascular risk factors, it appears to act, at least partially, independent of the other risk factors. In actual fact, it is much more predictive of cardiovascular events and mortality in women and in men with fewer risk factors.

This new information makes it necessary that we reassess how we utilize SUA in underwriting. It is an inexpensive test as it is offered by insurance laboratories as part of the fixed price blood profile. So the cost of the test is not a factor in assessing its utility. The main consideration is designing a role for SUA that is appropriate to its significance as a risk factor.

One such role is as a screening test. In this role it would be used in combination with other tests such as lipids, eGFR, microalbumin and Hemoglobin A1c to select problem cases for further scrutiny. Based on predetermined cutoff values for each of these tests, alone or in combination, additional requirements such as medical records, brain natriuretic peptide

(BNP), echocardiogram or stress testing could be requested.

SUA also could be utilized to rate cases when the test result is significantly elevated or when cases are being underwritten with limited requirements. In this circumstance an additional rating would be applied based on the SUA level.

The exact means by which UA causes disease and increases mortality will be debated for some time. Nevertheless, there is little doubt of the association of hyperuricemia with increased incidence of hypertension, metabolic syndrome, type-2 diabetes, CAD, stroke and increased CVD mortality. Whether this association is causative or not, it appears to precede and predict these events. Therefore it is appropriate to utilize SUA more widely in the selection of cardiovascular risks for life insurance. ♦

## Thymoma and Thymic Carcinoma

Thymoma is a tumor of the epithelial cells of the thymus. It accounts for 20 percent of all tumors of the mediastinum and is the most common tumor of the anterior mediastinum. Overall it is considered a rare malignancy with an incidence of 0.15 per 100,000. Most thymomas are slow growing with an indolent course; invasive thymomas and thymic carcinomas are rare.

**“Most cases of thymoma present in stages 1 and 2 and histological classification type A, AB or B1. These cases have a good prognosis.”**

Thymoma is usually diagnosed in the fourth or fifth decade of life. In 30 percent of cases, it is detected as an incidental finding in asymptomatic individuals. Presenting symptoms in the rest of the cases include cough, chest pain and upper airway congestion. The association of thymoma and myasthenia gravis is familiar to most underwriters.

Thymoma is also associated with many autoimmune disorders such as pure red cell aplasia and hypogammaglobulinemia. Additionally, those with a history of thymic tumor are at an increased risk for a second cancer; this risk is not the result of the treatment for thymoma.

The World Health Organization classification of thymoma (table 7) is widely accepted as the standard. This classification, along with the Staging System of Masaoko (table 8), is the basis of determining prognosis of this tumor.

Most cases of thymoma present in stages 1 and 2 and histological classification type A, AB or B1. These cases have a good prognosis. Because of the risk of second malignancies and late recurrences, all cases of thymoma need lifelong medical follow up. The more advanced stages, and types B2, B3 and C histologies, are a higher risk and need careful underwriting; coverage may need to be postponed.

Surgical resection is the preferred treatment and is feasible in most stage 1 and 2 patients. Postoperative radiation therapy may be needed in addition to surgery for stage 2 and 3 cases to destroy residual cancer cells. The aim of therapy in those with more advanced disease is symptom relief as

Table 7. Classification of Thymoma/Thymic Carcinoma

Thymoma	Other Names	Incidence of Myasthenia Gravis	Tumor Related Survival
Type A	Spindle cell or medullary	~ 17%	15+ year survival, close to 100%
Type AB	Mixed	~ 16%	15+ year survival, ~ 90%
Type B1	Lymphocytic or organoid	~ 57%	20+ yr. survival 90%
Type B2	Cortical or polygonal cell	~ 71%	20 yr. survival ~ 60%
Type B3	Epithelial, atypical, squamoid or well differentiated thymic carcinoma	~ 46%	20 yr. survival ~ 40%
Type C	Thymic carcinoma	0%	5 yr. survival 38%, 10 year survival 28%

Source: Thymoma and Thymic Carcinoma (PDQ<sup>®</sup>, <http://www.cancer.gov>)

Table 8. Thymoma Staging System of Masaoko

Stage	Description	5 year survival	20 year survival
I (Non Invasive)	Completely encapsulated, no capsular invasion	96%	89%
II (Locally Invasive)	Invasion of the capsule or surrounding tissues	86%	91%
III	Invasion into neighboring organs (pericardium, lung or great vessels)	69%	49%
IVa	Diffuse pleural and pericardial dissemination	49%	0%
IVb	Spread through the lymphatics or blood		

cure is not possible. Radiation therapy, debulking surgery (where the surgeon removes as much tumor as possible without disturbing or harming the surrounding area) and chemotherapy are prescribed as the situation warrants. ♦

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