Serum Uric Acid and Related Factors in 500 Hospitalized Subjects

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The study purpose was to determine the following in a large sample of hospitalized patients: (1) the prevalence of hyperuricemia, (2) the association of hyperuricemia with other metabolic disorders, and (3) the factors independently predicting hyperuricemia. Five hundred adult patients (250 men and 250 women) were randomly selected from those admitted as inpatients over a period of 5 months. In all patients, body mass index (BMI), blood pressure, and serum glucose, lipid, creatinine, urea nitrogen, and urate concentrations were measured. The presence of diseases or use of medications known to affect serum urate levels were recorded. The mean level of serum urate was 5.6 mg/dL in the whole sample, 6.0 mg/dL in men and 5.3 mg/dL in women (P = .003, men *v* women). The prevalence of hyperuricemia was 27.6% (28.8% and 26.4% in men *v* women, P = nonsignificant). A definite or probable secondary hyperuricemia was found in 87.7% of the subjects. Hyperuricemia was rarely isolated (21%), whereas it was frequently associated with hypertension (60.1%), hyperlipidemia (31.2%), diabetes (28.3%), and obesity (21.7%). In 26.8% of the subjects, hyperuricemia was associated with two metabolic disorders, in 13.8% with three, and in 2.9% with four. Multiple metabolic disorders (three to four) were found in 16.7% of subjects with hyperuricemia. Serum urate levels progressively increased across a range of subjects from those without diabetes, hyperlipidemia, hypertension, or obesity to those with one, two, or a greater number of associated metabolic abnormalities. Multiple stepwise regression analysis showed that 43% of serum urate variability was explained by urea nitrogen levels, triglyceride levels, diuretic therapy, the inverse of creatinine (as an index linearly related to creatinine clearance), and BMI. These results indicate that in hospitalized subjects, hyperuricemia is (1) frequent, (2) a secondary phenomenon in most cases, and (3) frequently associated with other metabolic disorders. The major predictors of high serum urate levels are BMI, triglycerides, parameters of renal function, and use of diuretics. These variables explain a large proportion of serum urate variability.

HYPERURICEMIA is a metabolic disturbance frequently occurring in the general population.[1-6] The overall prevalence observed in the Tecumseh and Framingham studies was approximately 5%.[1,2] This prevalence is expected to be much higher in hospitalized patients, but few studies have focused on this issue.[7]

Although it is not easy to distinguish between primary and secondary hyperuricemia, in the majority of cases hyperuricemia seems to be a secondary phenomenon[8] sustained by underlying diseases or exogenous factors, such as medication or alcohol intake, that increase the synthesis and/or reduce the renal excretion of uric acid. In a minority of cases, hyperuricemia is thought to be a primary abnormality.[8] However, this issue has received little attention, and the relative role exerted by factors influencing serum urate levels is poorly understood.

Other metabolic disorders such as non–insulin-dependent diabetes mellitus, obesity, hypertriglyceridemia, and hypertension are frequently associated with hyperuricemia.[4-6,9-12] These disorders frequently cluster within the same individual in the so-called "syndrome X" or "insulin resistance syndrome."[13-16] Since hyperuricemia has been associated with high insulin levels[17-19] and since insulin seems to be involved in the regulation of uric acid excretion,[20-22] a high serum urate concentration has been listed among the components of the insulin resistance syndrome. However, the number of studies formally exploring the association of hyperuricemia with the other members of this syndrome is insufficient.

The present study was undertaken in a large sample of hospitalized subjects to determine (1) the prevalence of hyperuricemia, (2) the association of hyperuricemia with other metabolic disorders, and (3) the factors independently predicting hyperuricemia.

SUBJECTS AND METHODS

Five hundred subjects (250 men and 250 women) aged 19 to 95 years were randomly chosen from those admitted as inpatients to the First Division of Internal Medicine of the Hospital of Mantua (a town of about 50,000 inhabitants of Northern Italy) from September 1993 to January 1994.

In all the patients, weight and height were measured at the time of admission, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. On the morning of the following day after a 12-hour overnight fast, venous blood was drawn to determine serum urate,[23] cholesterol,[24] triglycerides,[25] glucose,[26] creatinine,[27] and urea nitrogen.[28] Intraassay and interassay coefficients of variation for the urate assay were 1.2% and 1.9%, respectively. Blood pressure was measured by a mercury sphygmomanometer, with the subjects recumbent for at least 10 minutes and with Korotkoff phase 5 as the criterion for diastolic blood pressure.

The presence of the following metabolic disorders was established: obesity (BMI $\geq$ 30 kg/m^2)[29] (n = 59), hyperlipidemia (cholesterol $\geq$ 240 mg/dL and/or triglycerides $\geq$ 250 mg/dL or current therapy with hypolipidemic drugs)[30,31] (n = 123), diabetes (fasting serum glucose $\geq$ 140 mg/dL and/or current therapy with hypoglycemic drugs)[32] (n = 103), hypertension (systolic blood pressure $\geq$ 160 mm Hg and/or diastolic blood pressure $\geq$ 95 mm Hg or current therapy with hypotensive drugs)[33] (n = 212).

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In addition, the presence of the following diseases was recorded upon hospital admission and upon discharge from the hospital: heart failure (ICD-9 428, n = 168), chronic obstructive lung disease (ICD-9 490-493, n = 87), renal failure (ICD-9 584 and 585, n = 60), hematologic disorders (ie, myeloproliferative chronic diseases, leukemias, lymphomas, etc.; ICD-9 200 to 208, 238.4, and 238.7, n = 24), malignancies (ICD-9 140 to 199, n = 68), acute infections (ICD-9 1 to 136, n = 82), and chronic inflammatory diseases (ICD-9 446, 555, 556, and 710, n = 24). Finally, cachexy (BMI < 19 kg/m^2 due to severe chronic diseases, ie, malignancy, dementia, or heart, liver, or kidney failure, n = 52), dehydration (osmolality > 320 mOsm/kg H_2O, n = 18), alcoholism (chronic alcohol intake > 80 g/d, n = 83), malnutrition (estimated energy intake < 600 cal/d for ≥ 1 week before admission, n = 11), and chronic use of diuretics, corticosteroids, salicylates, or chemotherapeutic drugs in the 2 weeks before admission were recorded.

Hyperuricemia was diagnosed when serum urate concentration was at least 7 mg/dL in men and 6.5 mg/dL in women and/or when therapy with antihyperuricemic drugs was in progress. Hyperuricemia was considered primary when none of the clinical conditions known to increase serum urate were present, and secondary in other cases.[8] Three patients were hospitalized because of acute gouty arthritis.

The data were analyzed using the following statistical tests: unpaired Student's *t* test, one-way ANOVA, chi-square test, simple linear regression analysis, and stepwise multiple regression analysis. Nonparametric statistical tests were also used, but since these tests yielded results similar to those obtained with parametric tests, the results obtained with the latter are presented. All the statistical analyses were performed using StatViewSE+Graphics System statistical package (Berkeley, CA). In the statistical analyses, the logarithm for the triglycerides (because of the non-gaussian distribution of the frequence for this variable) and the inverse of serum creatinine (as an index linearly related to creatinine clearance)[34] were used. Data are presented as the mean ± SD. *P* values less than .05 were considered statistically significant.

RESULTS

Table 1 shows the main clinical and biochemical features of the subjects. The mean serum uric acid level was 5.6 mg/dL in the whole sample, 6.0 mg/dL in men and 5.3 mg/dL in women (P = .003, men *v* women). The frequency distribution for serum uric acid concentration is reported in Fig 1. There were few subjects (n = 13, 10 women and three men) with very low serum urate (<2 mg/dL). Of these, five had malignancies, four had acute infections, two had heart failure, one had diabetes mellitus, and one had depression.

Table 1. Main Clinical and Biochemical Characteristics of the Subjects

Characteristic	All (N = 500)	Men (n = 250)	Women (n = 250)
Age (yr)	68 ± 15	66 ± 16	70 ± 15*
BMI (kg/m^2)	24.2 ± 5	24.9 ± 5	23.6 ± 5*
Systolic BP (mm Hg)	145 ± 23	144 ± 22	146 ± 25
Diastolic BP (mm Hg)	84 ± 11	84 ± 10	85 ± 12
Fasting glucose (mg/dL)	114 ± 71	117 ± 83	111 ± 57*
Total cholesterol (mg/dL)	193 ± 58	185 ± 52	201 ± 63
Triglycerides (mg/dL)	137 ± 77	141 ± 81	134 ± 74
Creatinine (mg/dL)	1.20 ± 0.6	1.25 ± 0.6	1.14 ± 0.6*
Urea nitrogen (mg/dL)	21.3 ± 14	21.3 ± 13	21.3 ± 14
Urate (mg/dL)	5.6 ± 2.6	6.0 ± 2.6	5.3 ± 2.5†

Abbreviation: BP, blood pressure.
*P < .05, †P < .01: *v* men after adjustment for age.

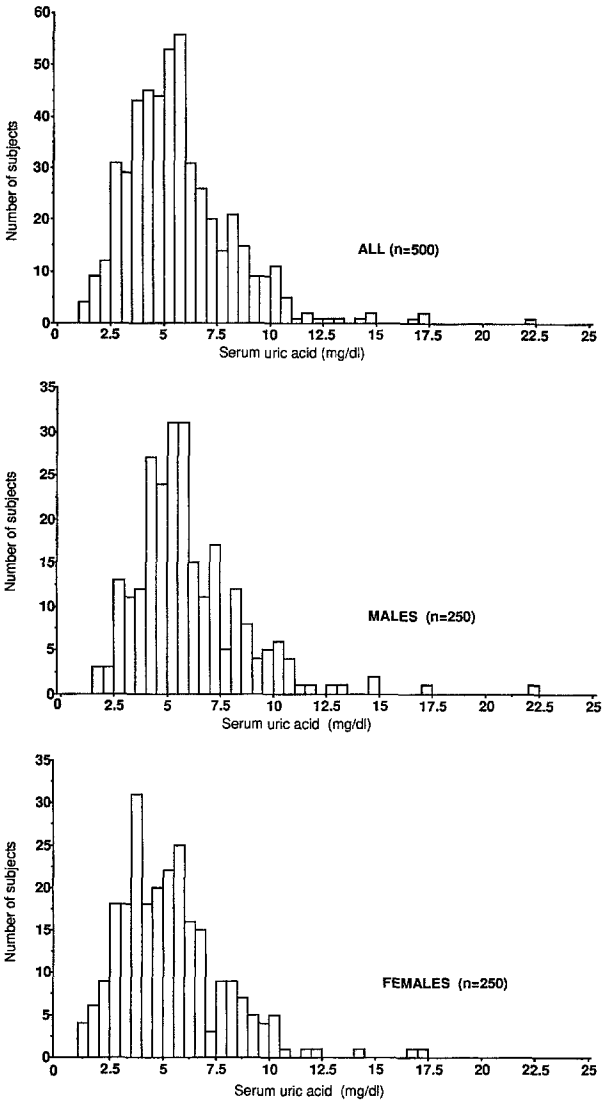

Fig 1. Frequency distribution for serum urate in all subjects and in men and women separately.

The prevalence of hyperuricemia was 27.6% (28.8% in men and 26.4% in women). A definite or probable secondary hyperuricemia was found in 87.7% of the subjects, without any significant difference between men (85%) and women (90.9%).

Hyperuricemia was rarely isolated (21%); it was instead frequently associated with hypertension (60.1%), hyperlipidemia (31.2%), diabetes (28.3%), and obesity (21.7%). On the other hand, hyperuricemia was more frequent in obese than in non-obese subjects (50% *v* 25%, P = .0002), in hypertensives versus normotensives (39% *v* 19%, P = .0001), in diabetics versus nondiabetics (38% *v* 25%, P = .008), and in hyperlipidemics versus normolipidemics (35% *v* 25%, P = .04). In 26.8% of the subjects, hyperuricemia was

associated with two metabolic disorders, in 13.8% with three, and in 2.9% with four. Multiple disorders (three to four) were found in 16.7% of subjects with hyperuricemia. Serum urate progressively increased across subjects, from those with no diabetes, hyperlipidemia, hypertension, or obesity to those with one, two, or more associated abnormalities (Fig 2).

Simple linear regression analysis (Table 2) showed significant associations of serum urate concentration with age, BMI, diastolic blood pressure, serum glucose, triglycerides, the inverse of creatinine, and urea nitrogen both in all subjects and separately in men and women. When subjects with cachexia (n = 52) were excluded from this analysis, serum urate was more strongly correlated with BMI ($r = .24$, $P < .0001$).

Serum urate was significantly increased in subjects with heart failure, chronic obstructive lung disease, renal failure, cachexy, or dehydration, and in those taking diuretic drugs (Table 3). Similar results were obtained after stratifying for sex (data not shown).

Multiple stepwise regression analysis (Table 4) showed that 46% of serum uric acid variability was explained by nine variables. In particular, urea nitrogen, diuretic therapy, triglycerides, BMI, and the inverse of creatinine explained approximately 43% of serum urate variability. The other four variables (chronic obstructive lung disease, cachexy, sex, and dehydration), although significant independent predictors of serum urate, only marginally explained its variability.

DISCUSSION

In this study, we found that the mean serum urate level in a large sample of adult hospitalized subjects was 5.6 mg/dL, about 0.5 to 1 mg/dL higher than that reported in other epidemiologic studies.[1-6] We believe this difference is due mostly to the fact that subjects in our study were hospitalized and older than those examined by others. For the same reason, the prevalence of hyperuricemia that we observed (27.6%) was higher than that reported by others (5% to 17%).[1-6] Indeed, the prevalence of hyperuricemia that we found was even higher than that reported by Paulus et al[7] in hospitalized patients. However, their subjects were younger and apparently less seriously ill than those included in our study.

Consistent with other reports, the mean serum uric acid concentration was 0.5 mg/dL higher in men than in women.[1-6] This difference is thought to reflect the different hormonal status of men and women. Indeed, renal excretion of uric acid is reduced by androgens and increased by estrogens.[35,36] Although most of the women examined in the present study had been in the postmenopausal state for a

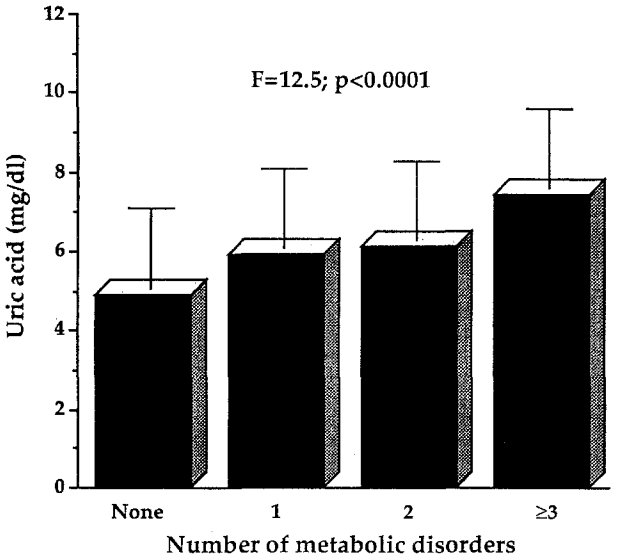

Fig 2. Serum urate concentration (mean ± SD) in relation to the number of associated metabolic disorders (ie, obesity, diabetes mellitus, hyperlipidemia, and hypertension) in 500 hospitalized patients.

Table 2. Simple Correlation Coefficients for Serum Urate Concentration and the Indicated Variables Both in Pooled Subjects and in the Two Separate Populations (N = 500)

Variable	All		Men		Women	
	r	*P*<	*r*	*P*<	*r*	*P*<
Age	.15	.001	.15	.01	.23	.001
BMI	.19	.0001	.20	.001	.14	.02
Systolic BP	.07	NS	.10	NS	.06	NS
Diastolic BP	.11	.02	.12	.05	.12	.05
Fasting glucose	.21	.0001	.20	.001	.23	.001
Total cholesterol	.03	NS	.02	NS	.08	NS
Log triglycerides	.26	.0001	.18	.005	.36	.0001
Inverse of creatinine	−.47	.0001	−.38	.0001	−.60	.0001
Urea nitrogen	.51	.0001	.46	.0001	.57	.0001

Table 3. Serum Urate Concentration According to Concurrent Disease and Drug Use in the Whole Sample

Disease/Drug	No	Yes	*P*
Disease			
Heart failure (n = 168)	5.2 ± 2.3	6.5 ± 3.0	.0001
Chronic obstructive lung diseases (n = 87)	5.5 ± 2.5	6.6 ± 3.0	.0005
Chronic renal diseases (n = 60)	5.3 ± 2.1	8.4 ± 3.5	.0001
Hematologic disorders (n = 24)	5.7 ± 2.5	6.4 ± 2.7	NS
Malignancies (n = 68)	5.7 ± 2.5	5.4 ± 3.0	NS
Acute infections (n = 82)	5.8 ± 2.7	5.3 ± 2.0	NS
Chronic inflammatory diseases (n = 24)	5.7 ± 2.6	5.1 ± 2.0	NS
Cachexy (n = 52)	5.4 ± 2.5	6.6 ± 3.5	.01
Dehydration (n = 18)	5.5 ± 2.5	8.5 ± 3.8	.0001
Alcoholism (n = 83)	5.6 ± 2.5	6.1 ± 2.7	.06
Malnutrition (n = 11)	5.7 ± 2.6	6.6 ± 3.0	NS
Drug			
Diuretics (n = 137)	5.1 ± 2.2	7.1 ± 3.0	.0001
Corticosteroids (n = 52)	5.7 ± 2.5	6.1 ± 3.6	NS
Salicylates (n = 68)	5.6 ± 2.5	5.9 ± 3.0	NS
Chemotherapeutics (n = 8)	5.5 ± 2.6	4.1 ± 1.5	NS

Table 4. Multiple Stepwise Regression Analysis: Standardized Regression Coefficients for Serum Urate Concentration (as dependent variable) on Indicated Covariates (N = 500)

Covariate	Standardized Regression Coefficient	F	P
Urea nitrogen	.34	64.3	.0001
Diuretics	.22	41.5	.0001
Log triglycerides	.22	39.0	.0001
BMI	.16	19.0	.0001
Inverse of creatinine	−.16	16.0	.01
R^2		.43	

NOTE. The model also included the following variables: age, serum glucose, alcoholism, heart failure, chronic obstructive lung disease, dehydration, cachexy, and sex. The latter 4 variables were independently associated with serum urate, but with marginal significance.

long time, their blood ratio of testosterone to estradiol can be thought to be lower than that of men.[37]

Since the diagnostic criterion for hyperuricemia in women was set at a value 0.5 mg/dL lower than in men, the prevalence of hyperuricemia was similar in men and women.

In many hyperuricemic individuals suffering from diseases or taking drugs known to influence serum urate levels, it is hard to exclude the concomitant presence of primary abnormalities of uric acid synthesis and/or excretion. However, in our study, secondary hyperuricemia seemed much more frequent than primary hyperuricemia (88% *v* 12%). It is worth underscoring that in the only report examining hospitalized patients of which we are aware, Paulus et al[7] found prevalence rates (82% *v* 18%) similar to those we observed.

In our study, hyperuricemia was frequently (79%) associated with other metabolic disorders such as obesity, diabetes, hyperlipidemia, and/or hypertension. In particular, 60% of patients with hyperuricemia were also hypertensive, a result consistent with those obtained by other investigators.[4-6,9,12,17-19,22] Also, hyperlipidemia was frequently associated with hyperuricemia (31%). In particular, triglycerides were strongly and independently correlated with serum urate in the multivariate analysis. These data confirm the well-known association of hypertriglyceridemia with hyperuricemia,[8-10,12,18-21] which was found in about 75% of gouty patients.[38] Also, the associations we found between hyperuricemia and obesity (22% of the cases) or diabetes (28%) are in agreement with previous reports.[4-6,8,9,12,38,39] In subjects with hyperuricemia, the association with more than two other metabolic disorders was frequent (~17%), further supporting the concept that metabolic abnormalities often cluster within the same individual.[18-21] These findings highlight the clinical importance of determining hyperuricemia in patients with other metabolic disorders and vice versa.

Multiple stepwise regression analysis documented that beyond BMI and triglycerides, urea nitrogen, the inverse of creatinine, and diuretic therapy are strong predictors of increased serum urate levels. This finding confirms the close relation between renal function and serum urate.[7,8,40,41] Also, the relationship between diuretics and urate is consistent with other reports.[7,8] It is well known, in fact, that these drugs can decrease tubular secretion and/or increase tubular reabsorption of uric acid, thus reducing its renal excretion.[40]

Interestingly, the power to predict serum urate levels with urea nitrogen was 50% higher than with diuretic treatment, for which the independent association with serum uric acid was as strong as that for triglycerides and twofold stronger than that for BMI.

In conclusion, the present study documents that in hospitalized subjects hyperuricemia is (1) common, (2) a secondary phenomenon in most cases, and (3) frequently associated with other metabolic disorders. The major predictors of high serum urate are parameters of renal function, triglycerides, BMI, and use of diuretics. Overall, these factors explain more than 40% of serum urate variability.

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