Hyperuricemia in Patients With Hyperthyroidism Due to Graves' Disease

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The effects of hyperthyroidism on uric acid metabolism were investigated. First, the serum uric acid level was measured in 92 patients with hyperthyroidism due to Graves' disease, eight patients with subacute thyroiditis, six patients with hypothyroidism, and 70 sex- and age-matched controls. Second, the correlation between serum thyroxine (T_4) and serum uric acid was obtained in hyperthyroid Graves' disease patients before and during antithyroid drug therapy. Finally, uric acid clearance (C_{UA}) was determined in untreated patients with hyperthyroidism due to Graves' disease. Serum uric acid was significantly elevated in patients with hyperthyroidism, and the elevation correlated well with serum T_4 before treatment as a group and during treatment in each patient. A significant elevation of serum uric acid was not present in patients with a transient mild thyrotoxicosis due to subacute thyroiditis. Serum uric acid was significantly decreased in patients with hypothyroidism. Renal excretion of uric acid clearly increased in hyperthyroid patients, and C_{UA} also increased. The increase in C_{UA} corresponded to the increase in renal plasma flow (RPF), which was measured by *p*-aminohippuric acid clearance. The fractional excretion of uric acid as determined by C_{UA}/glomerular filtration rate (GFR) was similar and within the normal range in hyperthyroid patients and normal controls. A significant inverse correlation between C_{UA} and serum uric acid concentration was present in hyperthyroid patients as in normal controls, indicating that the renal handling of uric acid in the tubule affected uric acid excretion. However, the regression line of the correlation between C_{UA} and serum uric acid in hyperthyroid patients was steeper than that in controls, with the contiguous intercept on the abscissa. We conclude that the serum uric acid concentration increased in hyperthyroidism due to an increased production that surmounted the increase in C_{UA}.

A NUMBER OF METABOLIC processes are accelerated in the hyperthyroid state due to Graves' disease. For example, protein metabolism is accelerated in hyperthyroid patients, and low-normal values of serum albumin and subnormal values of thyroxine (T_4)-binding globulin are found in thyrotoxic patients.[1-5] Although particular attention has rarely been paid to the metabolism of purine and its derivatives, it is conceivable that purine metabolism is also enhanced in hyperthyroidism. Actually, we have frequently encountered moderate hyperuricemia in hyperthyroid patients without any known history of gout or medication that would cause hyperuricemia. Furthermore, treatment of hyperthyroidism with methimazole accompanied a normalization of the serum uric acid concentration in these patients. Since a systematic study of uric acid metabolism in hyperthyroidism had not been performed, we analyzed a large number of hyperthyroid patients before treatment, during treatment, and after restoration of the euthyroid state to determine whether thyroid hormone excess did in fact cause hyperuricemia. We also performed a clearance study to evaluate the renal handling of uric acid in hyperthyroidism.

SUBJECTS AND METHODS

In the first part of the study, 66 female hyperthyroid patients (aged 10 to 79 years) and 26 male hyperthyroid patients (aged 12 to 60 years) were evaluated. For comparison, eight female patients with subacute thyroiditis and six female patients with severe hypothyroidism were also studied. As a control group, 49 normal female subjects (aged 13 to 77 years) and 21 normal male subjects (aged 12 to 76 years) were evaluated. In the second part of the study, a clearance study was performed in four untreated hyperthyroid patients and five normal, age-matched male control subjects. In the clearance study, inulin, *p*-aminohippuric acid, and uric acid clearances were determined as reported previously.[6]

The diagnoses of hyperthyroidism and hypothyroidism were made by clinical findings and laboratory data such as serum T_4, triiodothyronine (T_3), and thyrotropin (TSH) levels and 4-hour thyroidal radioiodine uptake.[7,8] Subacute thyroiditis was diagnosed when a painful goiter was present with elevated serum T_4 and T_3 concentrations, suppressed TSH levels, elevated erythrocyte sedimentation rate, leukocytosis, negative thyroidal autoantibodies including antimicrosomal, antithyroglobulin, and anti–TSH-receptor antibodies, and depressed thyroidal radioiodine uptake. Patients with hyperthyroidism were treated initially with 30 mg methimazole daily. The dose was reduced gradually depending on serum T_4, T_3, and TSH concentrations.[7,8] Serum T_4, T_3, and TSH levels were measured by radioimmunoassay using commercially available kits as reported previously.[7,8] Serum uric acid, creatinine, and blood urea nitrogen (BUN) levels were measured by an autoanalyzer.[6]

Statistical analysis was performed using Wilcoxon's rank-sum test, and *P* values less than .05 were considered statistically significant.

RESULTS

Serum Uric Acid Concentration Before Treatment, During Treatment, and After Restoration of the Euthyroid State in Hyperthyroid Patients

The serum uric acid concentration in all normal female subjects was lower than 6.0 mg/dL (Fig 1). In contrast, among 66 female untreated hyperthyroid patients, 15 patients (22.7%) had values exceeding 6.5 mg/dL and 26 (39.4%) had values above 6.0 mg/dL. Serum uric acid concentrations in 40 patients (60.6%) remained below 6.0

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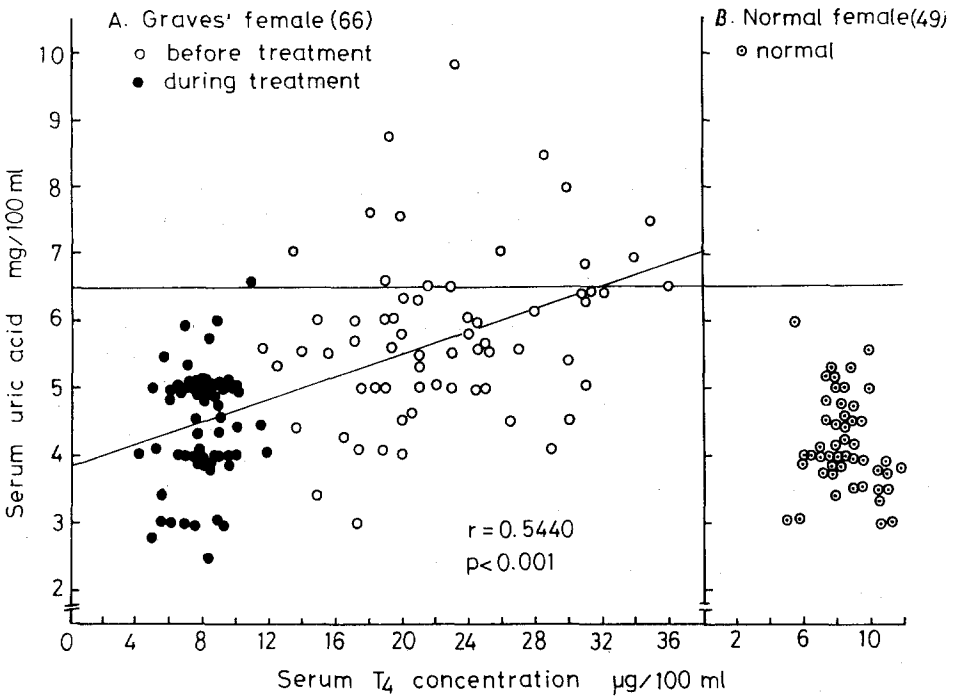

Fig 1. Correlation between serum T_4 and uric acid concentrations in (A) female patients with Graves' disease and (B) normal female subjects. Number of subjects is indicated in parentheses. There is a significant positive correlation in hyperthyroid patients.

mg/dL. As a result, the mean serum uric acid level in female untreated hyperthyroid patients was significantly higher than that in control females (Table 1). Before treatment, the serum uric acid concentration correlated well with the serum T_4 concentration (Fig 1A). Six months after treatment when the euthyroid state had been restored, the mean serum uric acid level was not significantly different from that of controls (Table 1, Fig 1A).

The serum uric acid concentration was higher in normal male subjects than in normal female subjects, but it was not statistically significant, since it was consistent with the commonly accepted findings[9] (Table 1). When male hyperthyroid patients were compared with normal male subjects, the mean serum uric acid level of hyperthyroid patients was significantly higher than that of normal male subjects. As in female patients, serum uric acid correlated well with serum

Table 1. Thyroid and Renal Function in Patients With Hyperthyroidism, Subacute Thyroiditis, and Hypothyroidism and Control Subjects

Group	n	Age (yr)	Uric Acid (mg/dL)	Creatinine (mg/dL)	BUN (mg/dL)	BUN to Creatinine Ratio	T_4 (μg/dL)	T_3 (ng/dL)	TSH (μU/mL)
I. Graves' disease									
a. Female									
Before Tx	66	42 ± 2	6.1 ± 0.2	0.64 ± 0.01	14.3 ± 0.5	22.9 ± 1.0	22.53 ± 0.78	405.0 ± 22.1	UD
After Tx			4.6 ± 0.1	0.82 ± 0.01	12.6 ± 0.4	15.4 ± 0.5	8.00 ± 0.23	113.3 ± 13.0	1.68 ± 0.25
b. Male									
Before Tx	26	37 ± 3	6.6 ± 0.2	0.74 ± 0.02	14.9 ± 0.7	20.7 ± 1.2	21.60 ± 1.17	470.7 ± 33.2	UD
After Tx			5.4 ± 0.2	0.96 ± 0.02	13.9 ± 0.5	14.4 ± 0.6	7.77 ± 0.31	17.2 ± 6.5	2.32 ± 0.56
II. Subacute thyroiditis	8	48 ± 2	4.5 ± 0.4	0.70 ± 0.03	14.5 ± 1.2	20.4 ± 1.6	12.67 ± 0.93	151.0 ± 11.1	0.67 ± 0.15
III. Hypothyroidism	6	40 ± 2	3.2 ± 0.1	1.05 ± 0.04	10.1 ± 1.0	10.0 ± 0.5	1.79 ± 0.23	57.3 ± 9.8	40.0 ± 2.3
IV. Control subjects									
a. Female	49	39 ± 2	4.2 ± 0.1	0.87 ± 0.01	13.0 ± 0.5	16.0 ± 0.6	8.47 ± 0.23	112.0 ± 5.2	2.0 ± 0.2
b. Male	21	38 ± 4	4.5 ± 0.2	0.92 ± 0.02	13.8 ± 0.8	15.1 ± 0.9	8.31 ± 0.31	108.1 ± 5.9	1.31 ± 0.14
Statistical analysis									
Ia									
Before *v* after			.001	.001	.05	.001	.001	.001	.001
Before *v* IVa			.001	.001		.001	.001	.001	.001
Ib									
Before *v* after			.001	.001		.001	.001	.001	.001
Before *v* IVb			.001	.01		.01	.001	.001	.001
After *v* IVb			.01						
III *v* IVa			.001						

NOTE. *P* values (less than) are shown only for comparisons with significant difference. Data are the mean ± SD. All patients in groups II and III are female.

Abbreviations: Tx, treatment; UD, undetectable.

T_4 in male patients before treatment (Fig 2). Six months after treatment when the euthyroid state had been restored, serum uric acid was significantly lower than the value before treatment. However, the mean value was still significantly higher than that of normal male subjects (Table 1).

In 11 hyperthyroid patients, serum uric acid concentrations were repeatedly determined during the methimazole treatment. As shown in Fig 3, serum uric acid decreased progressively in accompany with decreases in serum T_4.

In all patients, renal function was normal (BUN < 20 mg/dL and serum creatinine < 1.20 mg/dL; Table 1). However, the serum BUN to creatinine ratio was significantly elevated in untreated hyperthyroid patients, as in previous studies.[6,10]

Serum Uric Acid Concentration in Patients With Transient Mild Thyrotoxicosis and in Those With Severe Hypothyroidism

Among eight patients with subacute thyroiditis, serum uric acid concentrations were less than 6.5 mg/dL in all but one, although the mean serum uric acid concentration was slightly but insignificantly higher than that of normal female subjects (Table 1).

In six female patients with severe hypothyroidism, serum uric acid was in the low-normal range and the mean concentration was significantly lower than that of normal female subjects (Table 1).

BUN and serum creatinine concentrations were within the normal range in all patients with subacute thyroiditis and hypothyroidism. The BUN to creatinine ratio was higher in subacute thyroiditis and lower in hypothyroidism than in normal female subjects. The difference in the BUN to creatinine ratio between the control and hypothyroid groups was statistically significant. These findings were consistent with data reported by us and others previously.[6,10,11]

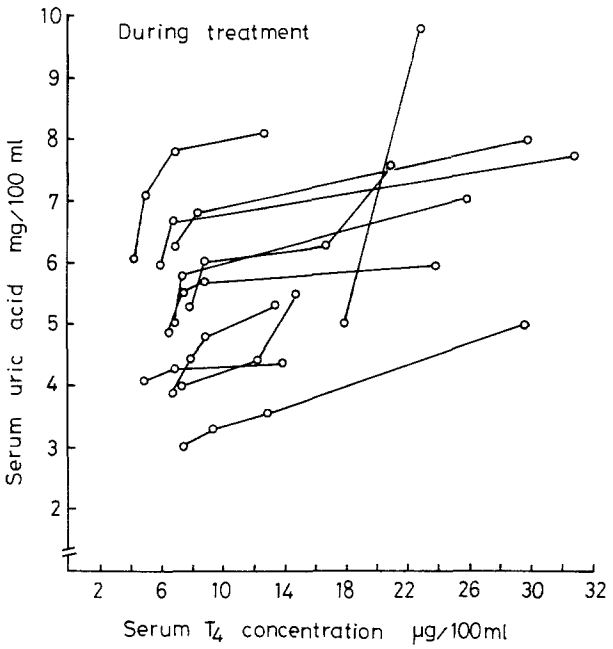

Fig 3. Serum uric acid and T_4 concentrations in 11 hyperthyroid patients during treatment with an antithyroid drug. Each line indicates a single patient.

Renal Uric Acid Clearance in Hyperthyroid Patients

A clearance study was performed in four untreated male patients with hyperthyroidism and five normal, age-matched male control subjects. As shown in Table 2, the

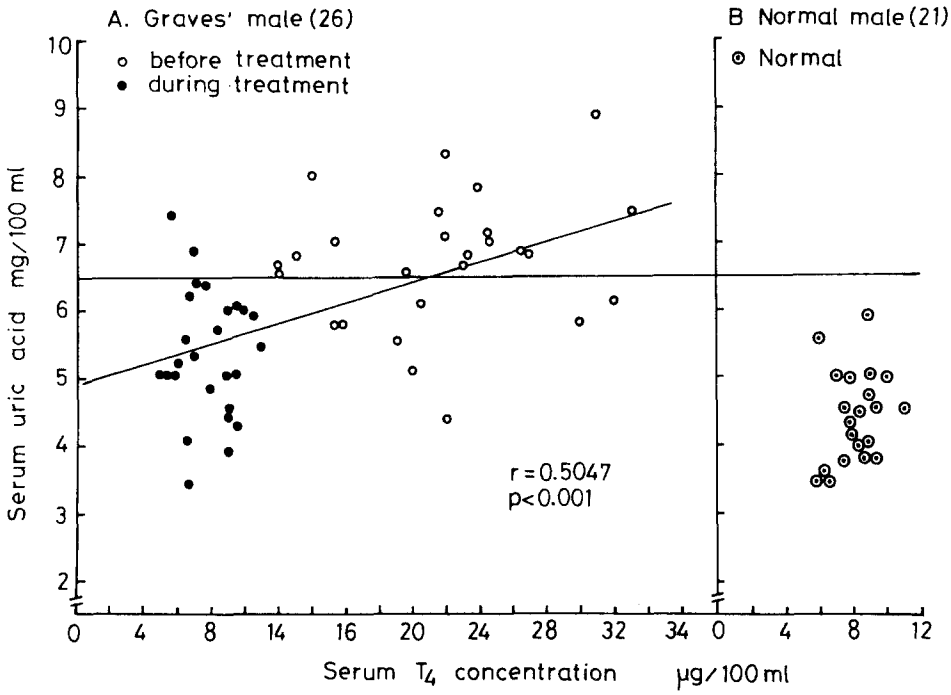

Fig 2. Correlation between serum T_4 and uric acid concentrations in (A) male patients with Graves' disease and (B) normal male subjects. Number of subjects is indicated in parentheses. There is a significant positive correlation in the patients.

Table 2. Results of Clearance Study

	Hyperthyroid Patients	Controls	*P*
n	4	5	
Age (yr)	29.8 ± 11.5	30.2 ± 7.2	NS
Serum T_4 (μg/dL)	18.6 ± 1.2	8.7 ± 0.8	<.001
Serum T_3 (ng/dL)	258.5 ± 37.1	112.0 ± 15.0	<.001
Uric acid excretion (mg/90 min)*	5.60 ± 1.63	3.22 ± 0.59	<.05
C_{UA} (mL/min)	8.8 ± 3.2	4.9 ± 1.1	<.05
GFR, C_{IN} (mL/min)	89 ± 19	76 ± 16	NS
RPF, C_{PAH} (mL/min)	662 ± 69	429 ± 149	<.05
Filtration fraction	0.135 ± 0.027	0.196 ± 0.082	NS
C_{UA}/GFR	0.104 ± 0.056	0.066 ± 0.015	NS
C_{UA}/RPF × 100	1.34 ± 0.53	1.23 ± 0.45	NS

NOTE. Data are the mean ± SD.

Abbreviations: C_{IN}, inulin clearance; C_{PAH}, *p*-aminohippuric acid clearance.

*Adjusted for body surface area (m^2).

glomerular filtration rate (GFR) as determined by inulin clearance and renal plasma flow (RPF) as determined by *p*-aminohippuric acid clearance were greater in hyperthyroid patients than in normal controls. RPF in hyperthyroid patients was greater than in controls and statistically significant. The filtration fraction was not significantly different between the two groups. Uric acid clearance (C_{UA}) was significantly greater in hyperthyroid patients than in controls. However, when C_{UA}/GFR and C_{UA}/RPF were calculated, there were no significant differences between hyperthyroid patients and controls (Table 2).

When C_{UA} was plotted against serum uric acid concentrations, there was an inverse correlation between the two determinants in hyperthyroid patients, as in controls (Fig 4). However, the regression line of the hyperthyroid patients was above that of the controls, implying that at a given serum uric acid concentration C_{UA} was greater in hyperthyroid patients than in controls (Fig 4).

DISCUSSION

Since an acceleration of the turnover rate of serum proteins such as albumin and T_4-binding globulin has been well-established in hyperthyroidism,[1-5] it is expected that purine metabolism is also accelerated in hyperthyroidism. However, studies on uric acid metabolism in hyperthyroidism have been very limited, although it was reported that the mean value for uric acid concentration was significantly higher when patients were hyperthyroid than when euthyroid, and many of the biochemical changes between the hyperthyroid and euthyroid states took place within the reference ranges.[10]

Our study performed in 92 patients with hyperthyroidism due to Graves' disease clearly established that moderate hyperuricemia was present in this disorder in the absence of gouty arthritis. It also demonstrated that the magnitude of serum uric acid elevation correlated well with the serum thyroid hormone concentration in hyperthyroid patients before and during treatment. In contrast, no significant increases in serum uric acid were found in transient mild thyrotoxicosis due to subacute thyroiditis. Therefore, an elevation of thyroid hormone that exceeds a certain level for a considerable period seems required to induce hyperuricemia in man. Although a substantial number of untreated female hyperthyroid patients had serum uric acid concentrations below 6.0 mg/dL, their mean value for serum uric acid significantly decreased after 6 months when the euthyroid state was restored and maintained by methimazole treatment, suggesting that even serum uric acid concentrations below 6.0 mg/dL might have increased mildly before treatment. The slightly higher serum uric acid level in male hyperthyroid patients after treatment may be due to a high uric acid production rate in males, and we believe it will eventually be normalized. Furthermore, the serum uric acid concentration was low in hypothyroidism. Thus, the data clearly indicated that thyroid hormone excess itself was responsible for an elevation of serum uric acid in hyperthyroidism. In addition, we confirmed that the serum creatinine concentration in hyperthyroid patients was significantly lower than when the patients became euthyroid and that of controls, and was comparable with the previous report[10] (Table 1).

In general, a reduction in body weight of about 8 to 10 kg

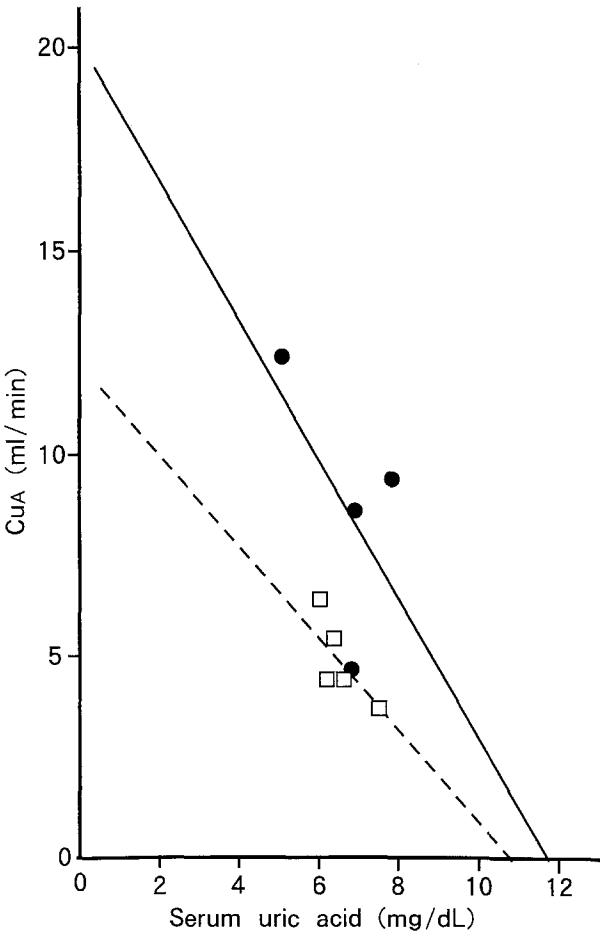

Fig 4. Correlations between C_{UA} and serum uric acid concentration in normal male subjects (□) and male untreated hyperthyroid patients (●). Negative correlations are shown by the regression lines: (—) patients ($r = -.5126$); (---) controls ($r = -.7729$).

is found in typical hyperthyroidism with increased appetite,[12] indicating that a marked catabolism of protein and other substances occurs in this disorder. Despite this, the increase in serum uric acid found here was moderate. Since the serum uric acid concentration is determined by the rate of production and renal excretion,[13,14] we performed a clearance study of uric acid in untreated patients with hyperthyroidism.

Uric acid excretion per unit time per unit body surface area in hyperthyroid patients significantly increased, consistent with the fact that urinary uric acid excretion increases parabolically in correlation with serum uric acid and is dependent on serum uric acid.[15] Furthermore, the increased uric acid excretion per unit time per unit body surface area indicated an increased production of uric acid. C_{UA} significantly increased in corresponding to the increases in RPF. However, the fractional excretion of uric acid as indicated by C_{UA}/GFR and also C_{UA}/RPF were similar between hyperthyroid patients and controls and were within the normal range. The inverse correlation of C_{UA} with serum uric acid shown in Fig 4 suggests that the renal handling of uric acid in the tubule affects uric acid excretion by decreasing secretion and/or increasing reabsorption.[6] Since most urinary uric acid in normal humans is the product of renal tubular secretion,[16-19] the relatively decreased renal tubular secretion may be a contributing factor in elevating serum uric acid, notwithstanding the increased C_{UA}. The regression line of C_{UA} with serum uric acid in hyperthyroid patients was above that in controls and was steeper than that in the controls with the contiguous intercept on the abscissa. This indicates that at a given serum uric acid concentration, hyperthyroid patients required more C_{UA} than controls.

On the basis of these data, we conclude that the serum uric acid level in hyperthyroidism increased due to the increased production of uric acid, which surmounted the increase in C_{UA}. The significant increase in C_{UA}, although affected by renal tubular secretion and/or reabsorption, is the likely reason for the only-moderate increase in serum uric acid in hyperthyroidism.

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