Hyperuricemia and gout in thyroid endocrine disorders

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Abstract

Objective

A significant correlation between thyroid function and purine nucleotide metabolism has been established in hypothyroidism. On the contrary, the relationship between hyperthyroidism and purine metabolism is more controversial. The present study evaluates the prevalence of hyperuricemia and gout in patients affected by primary hypothyroidism and hyperthyroidism.

Methods

We studied 28 patients with primary hypothyroidism and 18 patients with primary hyperthyroidism, all hospitalized because of endocrine dysfunction. All underwent a series of clinical, biochemical and instrumental evaluations; in particular, thyroid-stimulatin hormone (TSH), free thyroxine (fT4), blood urea, serum creatinine, creatinine clearance, serum and urinary uric acid levels were measured.

Results

In comparison to the prevalence reported in the general population, a significant increase of both hyperuricemia and gout was found in the hypothyroid patients, and of hyperuricemia in the hyperthyroid patients. In hyperthyroidism the hyperuricemia is due to the increased urate production, while in hypothyroidism the hyperuricemia is secondary to a decreased renal plasma flow and impaired glomerular filtration.

Conclusions

Our findings confirm the data in the literature concerning the high prevalence of hyperuricemia and gout in hypothyroidism. It shows that hyperthyroidism can cause a significant increase in serum uric acid, as well, although lower than the hyperuricemia due to thyroid hormone deficiency.

Key words

Hyperuricemia, gout, hypothyroidism, hyperthyroidism, pathogenesis.

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Introduction

The association between hypothyroidism and hyperuricemia was first suggested in 1955 by Kuzell and colleagues (1), who examined 520 patients suffering from gout and found hypothyroidism in 20% of the males and in 30% of the females. Subsequent studies (2-10) confirmed this association, furthermore suggesting that hypothyroid hyperuricemia could be due to a decrease in both the renal plasma flow and urate excretion (11-14).

On the contrary, the association between hyperthyroidism and hyperuricemia has always been more controversial. In 1989 Ford *et al.* (15),in contrast with previous reports (16, 17), demonstrated that hyperthyroidism can cause hyperuricemia through the increase of purine nucleotide turnover and the decrease of renal urate excretion. Other studies (18,19) confirmed their findings and also suggested that hyperthyroid hyperuricemia might be corrected by antithyroid drugs such methimazole. However, in 1999 Raber *et al.* (20) did not find any significant statistical difference in serum urate concentration between hyperthyroid patients and euthyroid ones.

Here we report our experience regarding the possible relationship between uric acid metabolism and thyroid disorders, presenting data obtained from patients suffering from either primary hypothyroidism or hyperthyroidism.

Patients and methods

Thirty-eight patients affected by primary hypothyroidism, 20 (71.4%) women and 8 (28.5%) men, aged between 34 and 81 years (average age, 65 ± 9.5 years), were examined. Eighteen primary hyperthyroid patients were studied as well, 14 (77.7%) women and 4 (22.2%) men, aged between 28 and 79 years (average age, 55 ± 8.3 years). All the patients were admitted to the Institute of Internal Medicine of the University of Siena during the period 1998 – 2000 due to signs and symptoms of thyroid dysfunction.

Hypothyroid patients (group A)

The hypothyroid patients presented the classic signs and symptoms of decreased secretion of thyroid hormone, in particular the manifestations of cardiovascular, central nervous and cutaneous system involvement. Moreover, they satisfied the biochemical criteria for the diagnosis of primary hypothyroidism (21), in particular, low serum levels of fT4 and increase titres of TSH. Patients with secondary (pituitary and hypothalamic) hypothyroidism, transient hypothyroidism,or a history of renal disease were excluded from the case study. In the 12 months preceding their admission, 7 (25.5%) of the 28 patients (5 women and 2 men) manifested relapsing monoarthritis, which was diagnosed as acute gouty attacks by their doctors. These 7 patients were treated with a non-steroidal antiinflammatory, but they had stopped any drug that might have interfered with uric acid metabolism at least 2 months before their admission to hospital. They were all on a normal purine diet.

The following laboratory tests were carried out: cytometric full blood count, total cholesterol, triglycerides, plasmatic electrolytes, serum creatinine and blood urea, creatinine clearance, serum uric acid, 24-hour urinary uric acid, thyroid-stimulation hormone (TSH), and free thyroxine (fT4) (TSH and fT3 were dosed by an automated chemiluminescence immunoassay). The following evaluations were also performed: blood pressure, electrocardiogram (ECG), echocardiogram, chest X-ray, renal and urinary tract sonograms and thyroid sonogram. The biochemical parameters (with the exception of thyroid hormones) were measured several times during each patient's hospitalization and 2 months after the beginning of the substitute hormone therapy with L-thyroxin (L-T4) (doses ranging between 75 and 100 g/day), while fT4 and TSH were measured at 0, 30 and 60 days from the beginning of L-thyroxin therapy. Thyroid sonogram, chest X-ray, echocardiogram and renal sonogram were carried out only once, at the moment of admission. ECG and blood pressure evaluations were verified frequently, and in particular at 30 and 60 days after beginning the hormone substitu-

tion therapy, in order to monitor the efficacy and tolerability of the treatment.

Hyperthyroid patients (group B)

The 18 hyperthyroid patients presented the classic signs and symptoms of increased secretion of thyroid hormone (Basedow's disease), in particular diffuse goiter and manifestations of cardiovascular and nervous system involvement. Moreover, they satisfied the biochemical criteria for the diagnosis of primitive hyperthyroidism (21): elevated serum levels of fT4 and low levels of TSH. Patients with other causes of thyrotoxicosis and patients with a history of renal insufficiency were excluded from this case study. None of the patients enrolled in the study presented signs or symptoms of gout, either previously or at the moment of hospitalization. All were on a normal purine diet.

The same battery of tests and examinations described above were carried out in this group of patients. Thyroid hormones were measured on day 0 and then two months after beginning the hormone suppression therapy with methimazole (attack dose: 15-20 mg/day; maintenance dose: 5-10 mg/day), using an automated chemiluminescence immunoassay.

Statistical analysis

The statistical evaluation of the results obtained was carried out using Student's t-test to analyse the significance of the difference between the averages of data paired under basal conditions, and before and after substitute hormone therapy with L-thyroxin (hypothyroid patients, group A) or suppressive therapy with metronidazole (hyperthyroid patients, group B), and Pearson's correlation coefficient to determine the possible correlations between the numerous variables on one side and TSH and fT4 on the other. The results were expressed as averages ± standard deviation (SD). Statistical significance was assigned as $p < 0.05$.

Results

Among the 28 hypothyroid patients, 2 (7.1%) (one male and one female) had monolateral gonarthritis at the moment of hospitalization. Both patients presented increased values of uric acid in the serum and of urate crystals in the joint fluid. In these 2 patients a diagnosis of gout was made and they were treated with colchicine (average dose: 3 mg/day, for 4 days). They had presented the same articular disease at home before their admission. Table I shows the demographic and laboratory data of the hypothyroid patients.

Table II describes the biochemical parameters in the 7 hyperuricemic hypothyroid patients under basal conditions and 2 months after L-thyroxin treatment. Among the hypothyroid patients, 9 (32.1%) presented stable hyperuricemia, a decrease in uric acid excretion (in 3 consecutive tests), increased creatinine, and decreased creatinine clearance (Table I). Six (66.6%) of these 9 patients were female, and 3 (33.3%) were male. A statistically significant difference was found between the 9 hyperuricemic hypothyroid patients and the 19 normouricemic hypothyroid patients as regards TSH, fT4, serum and urinary uric acid, serum creatinine, and creatinine clearance (Table I). Table II shows that the administration of L-thyroxin in the 9 hypothyroid-hyperuricemic patients resulted in the normalization of TSH, fT4 and serum and urinary uric acid levels, as well as of creatinine and creatinine clearance values. A statistically significant correlation was found between serum TSH and fT4 on the one hand, and creatinine clearance on the other ($p < 0.05$, Pearson's correlation coefficient) in the group of hypothyroid patients.

Table III shows the demographic and laboratory data on the 20 hyperthyroid patients. The results first of all demonstrate that 5 (27.7%) of the hyperthyroid patients presented stable hyperuricemia (demonstrated by at least 3 consecutive tests); these 5 patients were affected by asymptomatic hyperuricemia, and 3 (60%) of them were females. Of the 13 (72.2%) normouricemic hyperthyroid patients, 11 (84.6%) were females. Between the two groups of hyperthyroid patients, no significant difference was found as regards serum creatinine or creatinine clearance values. Table IV shows the values for the biochemical parameters in the 5 hyperuricemic hyperthyroid patients before and at the end of metronidazole treatment. The drug resulted in the normalization of fT4 and TSH values, and of the serum and urinary uric acid levels (Table IV). Lastly, in the hyperthyroid

Table I. Personal and biochemical data in patients (n = 28) with hypothyroidism, comprising 9 patients with increased serum uric acid levels and 19 patients with normal serum uric acid levels (expressed as means ± SD).

	Hyperuricemic (n = 9)	Normouricemic (n = 19)	P
Age (yrs.)	60.0 ± 3.4	61 ± 3.6	NS
Sex (no. of females)	6 (65.5%)	13 (68.4 %)	NS
TSH (nv 0.40-5.50 mUI/ml)	10.0 ± 1.2	7.5 ± 1.5	< 0.05
FT4 (nv 7.5-15 pg/ml)	3.9 ± 1.2	6.4 ± 0.9	< 0.05
Blood urea (nv 20-45 mg/dl)	53 ± 1.9	51 ± 2.3	NS
Serum creatinine (nv 0.5-1.2 mg/dl)	1.9 ± 0.2	0.7 ± 0.2	< 0.05
Creatinine clearance (nv 70-120 cc/min)	59 ± 4	94 ± 4.9	< 0.05
Serum uric acid (nv 3-7 mg/dl)	8.5 ± 1.2	4.8 ± 1.8	< 0.05
Urinary uric acid (nv 300-800 mg/ 24h)	280 ± 17.4	616 ± 21.1	< 0.001

patients no statistically significant correlation was found between TSH and fT4 on the one hand, and serum creatinine and creatinine clearance on the other.

Table II. Laboratory data in patients (n = 9) with hypothyroidism and hyperuricemia, before and after treatment (2 months) with L-thyroxin (expressed as means ± SD).

Parameter	Pre-treatment	Post-treatment	p
TSH (nv 0.40 - 5.50 mUI/ml)	10 ± 1.2	3.9 ± 1.4	< 0.001
FT4 (nv 7.5 - 15 pg/ml)	3.9 ± 1.2	10.6 ± 2.2	< 0.001
Blood urea (nv 20 - 45 mg/dl)	53 ± 1.9	32 ± 2	< 0.05
Serum creatinine (nv 0.5 - 1.2 mg/dl)	1.9 ± 0.2	0.8 ± 0.2	< 0.05
Creatinine clearance (nv 70 - 120 cc/min)	59 ± 4	101 ± 3	< 0.001
Serum uric acid (nv 3 - 7 mg/dl)	8.5 ± 1.2	5.1 ± 1	< 0.05
Urinary uric acid (nv 300-800\mg/ 24h)	280 ± 17.4	560 ± 15.1	< 0.001

Table III. Personal and biochemical data in patients (n = 18) with hyperthyroidism, comprising 5 patients with increased serum uric acid levels and 13 patients with normal serum uric acid levels (expressed as means ± SD).

	Hyperuricemic patients (n = 5)	Normouricemic patients (n =13)	p
Age (yrs.)	56 ± 3.3	55 ± 7.1	NS
Sex F	3 (60%)	11 (84.6%)	0.05
TSH (nv 0.40 - 5.50 mUI/ml)	0.30 ± 0.1	0.25 ± 0.1	NS
FT4 (nv 7.5-15 pg/ml)	19.4 ± 1.6	20 ± 1.7	NS
Blood urea (mean ± SD) (nv 20 - 45 mg/dl)	40 ± 0.9	41 ± 1.2	NS
Serum creatinine (nv 0.5 - 1.2 mg/dl)	0.9 ± 0.2	0.8 ± 0.3	NS
Creatinine clearance (nv 70 - 120 cc/min)	85 ± 1.3	89 ± 2.6	NS
Serum uric acid (nv 3 - 7 mg/dl)	7.9 ± 1.4	4.2 ± 1.2	< 0.05
Urinary uric acid (v.n. 280 - 800 mg/ 24 h)	855 ± 13.3	605 ± 16.2	< 0.05

Discussion

Our study evaluated the possible interrelationship between purine nucleotide metabolism and thyroid endocrine disorders, in particular primary hypo- and hyperthyroidism, by examining the data in the literature and comparing this with the data observed in a case study. In the literature, while the correlation between hypothyroidism and hyperuricemia is well established (1-14), the connection between hyperthyroidism and hyperuricemia still appears to be under debate (15-20).

The present study, even if based on a limited number of cases, showed a high prevalence of hyperuricemia in hypothyroid patients, 33.3%, which is substantially in accordance with the values reported by others (1, 3,7,8). This finding is particularly relevant when compared with the prevalence, ranging from 2 to 10%, in the general population (22, 23). Moreover, our study showed that hyperuricemia in hypothyroidism is associated with increased serum creatinine and decreased creatinine clearance. This fact suggests that hypothyroid hyperuricemia is secondary to a reduction in renal plasma flow and glomerular filtration, already well demonstrated in thyroid hormone deficiency syndromes (11-14).

The finding of a connection between gender and hypothyroid hyperuricemia seem to be important all the same. Our data and those in literature (3,4,7,8) indicate that hypothyroid hyperuricemia shows the same prevalence in both sexes, while it is known that hyperuricemia and gout are strongly associated with the male sex (22,23). The same prevalence of hypothyroid hyperuricemia in both sexes can be explained as follows: hypothyroidism is more frequent in females (21); hypothyroid hyperuricemia is due to a reduction in renal plasma flow and glomerular filtration secondary to thyroid hormone deficiency.

Examining the data on the hyperthyroid patients, the high prevalence of hyperuricemia appears evident: the prevalence was 27.7% in our case study, significantly higher than the prevalence of hyperuricemia in the general population (22). Our findings agree with those reported by some authors (15,18,19) but disagree with those described by others (20). At present, we are not able to completely explain these divergences: the selection criteria (outpatients or patients admitted to hospital) and different laboratory methods used to define THS and fT3 values (enzyme-linked immunoabsorption assays, radioimmunoassays,etc.) could explain in part the different results.

The increase in serum and urinary uric acid levels in our hyperthyroid patients

Table IV. Laboratory data in patients (n = 5) with hyperthyroidism and hyperuricemia, before and after treatment (2 months) with methimazole (expressed as the mean ± SD).

Parameter	Pre-treatment	Post-treatment	p
TSH (nv 0.40 - 5.50 mUI/ml)	0.30 ± 0.1	4.9 ± 1.6	< 0.001
FT4 (nv 7.5-15 pg/ml)	19.4 ± 1.6	13.5 ± 2.4	< 0.05
Blood urea (nv 20-45 mg/dl)	40 ± 0.1	39 ± 1.4	NS
Creatinine (nv 0.5-1.2 mg/dl)	0.9 ± 0.2	0.8 ± 1.1	NS
Creatinine clearance (nv 70-120 cc/min)	85 ± 1.3	93 ± 2.6	NS
Serum uric acid (nv 3-7 mg/dl)	7.9 ± 1.4	4.6 ± 1.3	< 0.05
Urinary uric acid (nv 300-800 mg/24 h)	855 ± 13.3	623 ± 16.6	< 0.05

seems to be due to accelerated purine nucleotide turnover. This hypothesis is shared by Sato and colleagues (19), but not by Di Shiroba and colleagues (18). In fact, Di Shiroba *et al.* (18) sustain that hyperthyroid hyperuricemia is secondary to the direct action of thyroxin on the kidney, consisting in a decrease in uric acid tubular excretion, not corrected by an increase of creatinine clearance. The significant increase in urinary uric acid levels in our hyperthyroid hyperuricemic patients seems to demonstrate that hyperthyroid hyperuricemia is linked to the increase in purine nucleotide turnover, rather than to a decrease in uric acid renal excretion. As was observed in the hypothyroid patients, in the hyperthyroid subjects as well hyperuricemia did not show a significant prevalence in the male sex. This finding can be explained by the high prevalence of hyperthyroidism in females and the increase in purine nucleotide turnover caused by thyroid hyperfunction.

With regard to the prevalence of gout in the two populations, we noted that no hyperuricemic patient had signs or symptoms of this metabolic disease. This fact could be due to the lower values of hyperthyroid hyperuricemia than those of hypothyroid hyperuricemia, as evidenced in our study.

Despite the small number of the patients examined, the present study shows that hyperuricemia is a common feature not only of hypothyroidism, but also of hyperthyroidism. Therefore, we would emphasize the importance of the routine evaluation of serum and urinary uric acid levels, both in patients affected by hypothyroidism and in patients with hyperthyroidism. In this way we will be able to correct the possibly altered purine nucleotide metabolism and to prevent the onset of gout, which can worsen thyroid endocrine disorders.

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