Dyshormonal Disorders in Gout: Experimental and Clinical Studies

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A total of 107 patients with primary gout were examined. The pituitary-gonadal system is imbalanced in male patients with gout, which manifests by hyperproduction of progesterone and suppressed production of testosterone and estradiol. These changes are more pronounced in patients with chronic arthritis and proteinuric nephropathy. Similar dyshormonal changes are experimentally simulated in rats by induction of purine metabolism disorders. Exogenous injection of androgens in experimental hyperuricemia led to normalization of purine metabolism and hormonal homeostasis.

Key Words: *gout; sex and gonadotropic hormones; purine metabolism*

The prevalence of gout among men in Europe is 0.1-0.7% [2,7,10]. The incidence of gout in some countries increased by more than 20% over recent 25 years [11,12]. Currently used methods of pathogenetic therapy are ineffective [1,2,6].

The relationships between purine metabolism disorders and hormone imbalance in male gout were widely discussed in recent years [5,7-9].

The aim of our study was to detect the type of dyshormonal disorders in experimental animals and in patients with gout and to improve treatment efficiency by hormonal correction.

MATERIALS AND METHODS

Experiments were carried out on random-bred albino rats. In group 1 (n=20) purine metabolism disorders were induced as described previously [3], in groups 2-4 (10 animals per group) purine metabolism disorders and urate arthritis were induced by intra-articular injection of 0.1 ml of urate crystal suspension. In groups 3 and 4 the disorders were corrected by intramuscular injections of 2% sinestrol (0.2 ml) or 1% testosterone propionate (1 ml) daily for 4 weeks. After the end of the experiment the rats were decapitated under ether narcosis, and blood concentrations of sex and gonadotropic hormones and uric acid were measured [4]. Intact rats (n=20) served as controls.

A total of 107 male patients with primary gout were observed. They were divided into 3 groups receiving the following treatment: 1) uricodepressive, uricosuric, and nonsteroid antiinflammatory drugs (n=30); 2) androgens (n=27); and 3) traditional therapy for gout+androgens (n=50). The treatment was based on compensation of testosterone deficiency in order to attain normalization of purine metabolism; androgens were prescribed only to patients with initial hypotestosteronemia. The treatment started with daily injections of 1% testosterone propionate (1 ml) for 4 weeks, which were then replaced with long-acting forms (sustanone-250 or tetrasterone, 1 ml intramuscularly once a month).

Blood concentrations of uric acid and oxypurinol, gonadotropic (lutropin, follitropin) and sex hormones (testosterone, estradiol, progesterone) were measured before and 6-9 months after the start of therapy. Uric acid and oxypurinol clearances were estimated routinely [4]. Control group consisted of 30 healthy age-matched men.

RESULTS

The treatment led to a statistically significant decrease in blood level of testosterone and an increase of pro-

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gesterone level in all patients. The most marked decrease of testosterone production was observed in patients with proteinuric nephropathy and chronic arthritis. Hyperlutropinemia was observed in all patients, with follitropin level remaining virtually unchanged (Table 1).

Changes in the pituitary gonadotropic function and level of sex hormones in rats were similar to those observed in humans. The level of uric acid in the blood increased to 690.2±8.19 mmol/liter in animals with experimental gout in comparison with the control (100.5±5.0 mmol/liter). Sinestrol decreased uricemia to 200.4±18.0 mmol/liter, and testosterone treatment resulted in complete normalization of uric acid content (120.9±14.0 mmol/liter). Injections of testosterone increased its blood concentration from 7.1±0.7 nmol/liter in the group without correction to 14.8±0.3 nmol/liter after treatment ($p< 0.001$), estradiol level increasing from 0.030±0.001 to 0.040±0.001 nmol/liter and that of progesterone decreasing from 0.54±0.03 to 0.32±0.03 nmol/liter ($p< 0.001$, Fig. 1). The results of experiments proved the validity of testosterone therapy in humans.

The number of involved joints (articular count) decreased 3-fold after therapy with sex hormones and only 1.5 times after traditional therapy. Androgen therapy had a positive impact on the nephrotic syndrome: the incidence of renal colics, severity of edema, and level of azotaemia decreased. In groups 2 and 3 the levels of uric acid in the blood notably decreased and its clearance increased (Table 1).

In group 1 the treatment promoted a decrease of progesterone level, while the level of testosterone remained unchanged (Table 1). In group 2 testosterone level increased and that of progesterone slightly decreased. In group 3 combined therapy was associated with a less pronounced increase of testosterone level (Table 1).

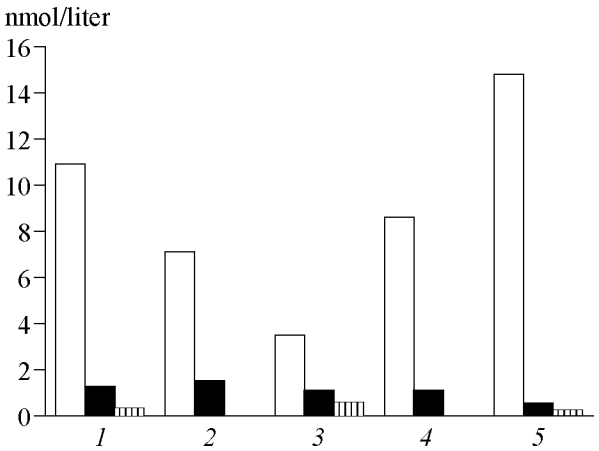

Fig. 1. Blood concentrations of testosterone (light bars), progesterone (dark bars), and estradiol (cross-hatched bars) in rats. *1*) intact animals; *2*) animals with disorders in purine metabolism; *3*) the same+urate arthritis: *4*, *5*) correction of hyperuricemia and urate arthritis by sinestrol and testosterone propionate, respectively.

During subsequent 6-9 months the number of patients with positive results of treatment increased 2-fold in group 3 in comparison with group 1. Only in 3 patients androgen therapy was associated with the appearance of striae and body weight increase, which required decrease of the dose and number of injections.

It was previously shown that testosterone synthesis decreased and progesterone production increased in gouty men [8]. Suppression of testosterone synthesis was observed in chronic arthritis and proteinuric nephropathy, the most unfavorable variants of the disease. Presumably, hyperuricemia modulated the hypothalamic secretion of lutropin, which resulted in de-

TABLE 1. Hormonal Homeostasis and Purine Metabolism in Male Patients with Gout before and after Treatment ($M\pm m$)

Parameter	Normal subjects (n=30)	Group 1 (n=30)		Group 2 (n=27)		Group 3 (n=50)	
		before therapy	after therapy	before therapy	after therapy	before therapy	after therapy
Testosterone, nmol/liter	21.90±0.92	8.12±1.06*	8.32±0.66*	10.76±2.34*	24.0±3.09*	9.51±1.33*	21.80±4.55^{+}
Estradiol, nmol/liter	0.09±0.01	0.12±0.01	0.10±0.02	0.26±0.07*	0.98±0.28*$^{+}$	0.40±0.08*	2.35±1.11*
Progesterone, nmol/liter	0.58±0.08	12.59±0.96*	1.03±0.31^{+}	10.60±1.53*	7.27±1.53*	15.40±2.51*	4.22±2.01^{+}
Uric acid, mmol/liter blood	0.27±0.02	0.54±0.03*	0.49±0.03*	0.45±0.02*	0.25±0.01*	0.55±0.02*	0.37±0.02*
Uric acid clearance, ml/min	10.9±0.4	6.7±0.8*	8.5±1.1*	8.1±0.7*	9.7±0.7	7.7±0.6*	8.6±0.9*
Oxypurinol, µmol/liter blood	20.4±4.4	120.9±17.1*	116.1±16.4*	89.5±10.6*	63.6±12.3*	98.5±8.2*	74.4±11.2*
Oxypurinol clearance, ml/min	24.4±0.6	15.9±1.6*	16.3±1.5*	17.6±0.9*	20.9±1.2*$^{+}$	17.4±0.7*	20.3±2.1

Note. $p<0.05$: **vs.* normal subjects, *$^{+}$vs.* parameters before therapy.

creased production of follitropin, and this, in turn, inhibited the production of testosterone.

Hence, the pituitary-gonadal system is imbalanced in male patients with gout. This presented as progesterone hyperproduction and suppressed production of testosterone and estradiol (in patients with chronic arthritis and proteinuric nephropathy). A similar hormone imbalance was experimentally induced by impairment of purine metabolism, which attests to the secondary nature of hormonal changes. Exogenous androgens in experimental hyperuricemia normalized purine metabolism and hormone homeostasis. Androgen therapy of patients with gout improved the results of treatment in general.

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