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BRIEF REPORT

EFFECT OF LONG-TERM ADMINISTRATION OF CROSS-SEX HORMONE THERAPY ON SERUM AND URINARY URIC ACID IN TRANSSEXUAL PERSONS

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Abbreviated title: Uric acid metabolism in transsexual persons

Key terms: transsexual, uric acid, fractional excretion of uric acid, cross-sex hormone treatment, metabolic syndrome, insulin resistance, diabetes mellitus, HOMA-IR

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ABSTRACT

Background: Transsexual persons afford a very suitable model to study the effect of sex steroids on uric acid metabolism.

Design: A prospective study to evaluate the uric acid levels and fractional excretion of uric acid (FEUA) in a cohort of 69 healthy transsexual persons, 22 Male-to-Female Transsexuals (MFT) and 47 Female-to-Male Transsexuals (FMT). The subjects were studied at baseline, and one year and two years after starting cross-sex hormone treatment.

Results: The baseline levels of uric acid were higher in the MFT group. Compared to baseline, uric acid levels had fallen significantly after one year of hormone therapy in the MFT group and had risen significantly in the FMT group. The baseline FEUA was greater in the FMT. After two years of cross-sex hormone therapy, the FEUA had increased in MFT ($p=0.001$) and fallen in FMT ($p=0.004$). In MFT, the levels of uric acid at two years were lower in those who had received higher doses of estrogens ($p=0.03$) and the FEUA was higher ($p=0.04$). The FEUA at two years was associated with both the estrogen dose ($p=0.02$) and the serum levels of estradiol-17 beta ($p=0.03$). In MFT, a correlation was found after two years of therapy between the HOMA-IR and the serum uric acid ($r=0.59$; $p=0.01$).

Conclusions. Serum levels of uric acid and the FEUA are altered in transsexuals as a result of cross-sex hormone therapy. The results concerning the MFT group support the hypothesis that the lower levels of uric acid in women are due to estrogen-induced increases in FEUA.

INTRODUCTION

Plasma uric acid concentrations are higher in men than age-matched women (1), possibly due to greater renal clearance of uric acid in women (2-4). The underlying mechanisms of this greater clearance are not fully known (4), though suggestions include the higher levels of estradiol (4-5) and a lower post-secretory tubular reabsorption of urate in women (6). Other studies defend the direct influence of insulin in the renal management of uric acid (7-10). As transsexual persons afford a very suitable model to attempt to clarify these questions, at least partly, we examined the long-term effect of sex steroids on serum concentrations and fractional excretion of uric acid (FEUA) in a cohort of MFT and FMT undergoing cross-sex hormone therapy.

MATERIAL AND METHODS

The study involved a cohort of 69 healthy transsexuals (22 MFT and 47 FMT), selected consecutively provided they fulfilled the diagnostic criteria of the Standards of Care of the WPATH (11), had not previously received cross-sex hormone treatment, and had no known metabolic or inflammatory disease. The study was approved by the hospital Ethics Committee and the participants gave written informed consent.

Once accepted into the program of the Andalusian Gender Team (AGT), the subjects started hormone therapy with a minimum two-year medical follow-up. The mean age of the MFT was 23.1±9.4 years and of the FMT 25.7±6.0 years. Of the MFT, 18 had received conjugated oral estrogens, one oral estradiol valerate and three transdermal estradiol patches. The daily estrogen dosage in the MFT was classified as: low (0.625-1.250 mg conjugated estrogens or 1-2 mg of oral estradiol valerate or 50 µg of transdermal estradiol), medium (1.875 mg conjugated estrogens or 3-4 mg of oral estradiol valerate or 75 µg of transdermal estradiol) and high (more than 1.875 mg conjugated estrogen or more than 4 mg of oral estradiol valerate or 100 µg of transdermal estradiol). A low dose is similar to that of HRT, medium dose twice that of HRT, and high dose above twice that of HRT (12-14). The number of MFT during the first year on low, medium or high doses of estrogens was 16, 6 and 0, respectively, and during the second year it was 13, 4 and 4, respectively. All the

MFT also received cyproterone acetate (50-100 mg per day).

In the FMT, during the first year 93.3% received 250 mg intramuscular testosterone enantate or propionate each two weeks, and 6.7% had 5 mg per day testosterone in patches. During the second year, 69.6% received injectable testosterone enantate or propionate and 30.5% received testosterone in patches or gel.

The main variables were analyzed at each of the three study phases (baseline, one year and two years after starting therapy). The anthropometric variables studied included weight and height (to calculate the body mass index (BMI) (kg/m^2)). The patients followed their usual diets throughout the study.

At each of the three study points a fasting blood sample was obtained between 8-10 a.m. and at least 12 hours after the last dose of estrogens in the MFT and 7 days after the parenteral administration of testosterone in the FMT. After separating the serum, the samples were analyzed immediately. Serum measurements included total testosterone and estradiol-17 beta (chemiluminescence), uric acid, creatinine, glucose (colorimetric enzymatic method) and insulin (immunoradiometric assay). The Homeostasis Model Assessment (15) was used with the serum glucose and insulin to assess the index of insulin resistance (HOMA-IR).

Measurements were made in a subgroup of the transsexuals (19 MFT and 25 FMT) of uric acid and creatinine concentrations in 24-hour urine samples (colorimetric enzymatic method). The fractional excretion of uric acid (FEUA) (%) was calculated at baseline and two years after starting cross-sex hormone therapy, according to the equation:

$$FEUA = \frac{UAu \times CREAs}{UAs \times CREAu} \times 100$$

where *UAu* is the uric acid in urine (mg/dl), *CREAs* is the creatinine in serum (mg/dl), *UAs* is the uric acid in serum (mg/dl) and *CREAu* is the creatinine in urine (mg/dl).

The statistical analysis was done with SPSS 11.5 for Windows. The quantitative variables are presented as means and standard deviations and the qualitative variables as proportions. The hypothesis contrast was made with the Student test for paired or unpaired samples, according to the nature of the variable, and comparison of more than two variables was made with a one-way ANOVA. The correlation between variables was made by calculating the

Pearson (r) correlation coefficient. In all cases the level of rejection of a null hypothesis was $\alpha \leq 0.05$.

RESULTS

The FMT had a significantly greater BMI than the MFT at all three study points. The BMI in the MFT remained unchanged throughout the study. In the FMT it increased significantly during the first year and remained stable during the second year (Table I).

As expected, the baseline levels of estradiol-17 beta were significantly higher in the FMT, but fell during the first and second years of androgen treatment. At the same time, a significant increase was seen in testosterone levels. The MFT showed a significant increase in levels of estradiol-17 beta one year after starting estrogen therapy, and a very significant decrease in testosterone levels, with similar levels after two years (Table I).

The baseline levels of uric acid were significantly higher in the MFT (Table I). One year after starting treatment the uric acid levels fell significantly in the MFT and increased significantly in the FMT. The uric acid levels differed significantly between the MFT and FMT after both one and two years.

The baseline FEUA was significantly greater in the FMT (Table I). Two years after starting therapy the FEUA had increased in the MFT ($p=0.001$) and fallen in the FMT ($p=0.004$). At this point, the FEUA levels were significantly greater in the MFT than in the FMT (Table I).

The levels of estradiol-17 beta one year after starting treatment were higher in the MFT treated with medium doses of estrogens than in those treated with low doses (67.22 ± 27.20 vs. 33.00 ± 25.14 pg/ml) ($p=0.01$).

The baseline levels of glucose were greater in the MFT, showing no significant changes over the study period. The baseline levels of insulin were no different between the two groups. However, one year after starting therapy these levels fell significantly in the FMT, remaining similar at the two-year point. Significant differences were found between the MFT and FMT groups after both one and two years (Table I).

The HOMA-IR was significantly greater in the MFT at all three study points. Compared with the baseline levels, the HOMA-IR fell significantly after one year in the FMT, but not

in the MFT, remaining similar after two years (Table I).

One year after starting therapy, the serum levels of testosterone in the FMT correlated with the testosterone dose received (r=0.41; p=0.004).

In the MFT, the levels of uric acid after two years were lower in those who had received higher doses of estrogens (p=0.03). The FEUA was greater in those treated with higher doses (p=0.04) (Fig. 1).

Two years after starting therapy, levels of estradiol-17 beta correlated positively with FEUA in the MFT (r=0.54; p=0.04). This correlation was absent in the FMT.

In the MFT, an ANOVA model showed that the FEUA at two years was associated with both the dose of estrogens (p=0.02) and the serum levels of estradiol-17 beta (p=0.03).

In the MFT, after one year, serum levels of estradiol 17-beta correlated with the HOMA-IR (r=-0.49, p=0.03). After two years, the HOMA-IR correlated with the serum uric acid (r=0.59; p=0.01). No significant correlation was found at any of the study points between HOMA-IR and FEUA.

DISCUSSION

The most important results from this study are that serum levels of uric acid and the FEUA are significantly altered as a result of cross-sex hormone therapy in persons with gender dysphoria and in an estrogen dose-dependent manner in MFT.

Nicholls et al. studied 22 MFT before and 10 weeks after treatment with estilbestrol or ethynilestradiol. They found a reduction in plasma levels of uric acid and an increase in renal clearance and FEUA (4). Theirs is the only study to examine the effect of sex steroids on uric acid in transsexuals. They found no association between uric acid levels and excretion with estrogen dose, probably because almost all the subjects received the same dose. Furthermore, they did not record the plasma levels of estradiol-17 beta, required to explain the effect of the estrogens on uric acid metabolism.

Our results concerning the MFT support the hypothesis that the lower levels of uric acid in women are due to the effect of estrogens on the post-secretory tubular reabsorption of uric acid (6).

The increased estrogen might improve insulin sensitivity resulting in increased FEUA

and decreased serum uric acid. Some studies, though not all, have found that estrogens increase peripheral insulin sensitivity (10,16). General population studies with a normal OGTT have found higher baseline levels of glycemia, uric acid and HOMA-IR in men (17) whereas after an OGTT in women an association was found between serum uric acid levels, insulin and HOMA-IR (9). Polderman et al. examined insulin sensitivity using a hyperinsulinemic-euglycemic clamp in 13 FMT and 18 MFT before and after four months of cross-sex hormone therapy; both groups showed a slight but significant reduction in insulin sensitivity after treatment (18). However, another more recent study involving 20 MFT and 17 FMT found that, after one year of cross-sex hormone therapy, insulin sensitivity was only altered in the MFT group (19). In our study, despite finding a weak statistical correlation between levels of estradiol-17 beta and HOMA-IR after one year's treatment, the transsexuals treated with estrogens experienced no change in their HOMA-IR, nor in BMI or glycemia levels, both variables closely associated with peripheral insulin resistance. It is therefore unlikely that, if changes occurred in peripheral insulin sensitivity, they were sufficiently important to influence the FEUA.

In the FMT we found no clear association between testosterone doses/levels and FEUA, probably because most of the transsexuals used the same dose and because serum testosterone levels at a particular time do not represent the "status" of androgen impregnation during cross-sex hormone therapy, especially in those taking intramuscular enantate or propionate. Another possibility is that the reduction in estrogens following cross-sex hormone therapy induces a decrease in FEAU and an increase in serum uric acid. Several authors have examined the influence of testosterone on uric acid levels, though the presence of such an association is still controversial (20-21). The FMT group experienced a significant fall in HOMA-IR after one year of treatment with testosterone, which does not agree with the suggestion that an increase in testosterone in healthy women causes hyperinsulinemia and insulin resistance (22). It is therefore very unlikely that the increase in serum levels of uric acid and the fall in FEUA in the FMT are due to the action of insulin; rather, it is secondary to androgen

treatment and/or the reduction in endogenous estrogens.

The results of this study may have some practical implications. Epidemiological studies suggest that serum uric acid may be an independent factor of CHD mortality (23) and it is associated with various inflammatory markers and cytokines (24). Increasing serum estrogen levels appear to decrease serum uric acid levels by increasing renal uric acid excretion in MFT. Additionally, the fact that FMT increase their uric acid levels suggests the convenience of evaluating uric acid levels during cross-sex hormone therapy in this group. However, the fact that the levels remained stable with effect from the first year tells us that this increase may have no clinical relevance, although a longer follow-up might be necessary to confirm the long-term safety of this therapy. And finally, the results show the different metabolic response in the two groups of transsexuals depending on the dose of cross-sex hormone therapy.

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FIGURE LEGEND

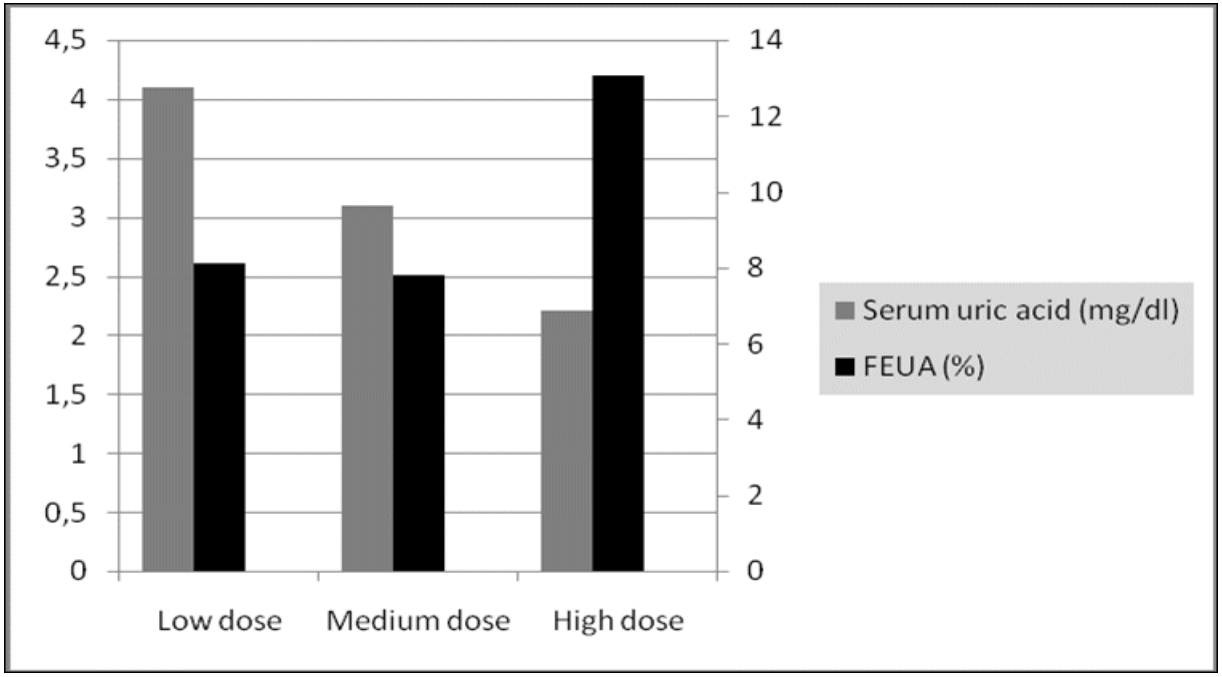
Figure 1: Serum levels of uric acid and fractional excretion of uric acid in relation with estrogen dose in MFT after two years of treatment. p=0.03 (for uric acid), p=0.04 (for FEUA).

Table I. BMI, serum levels of estradiol-17 beta, total testosterone and uric acid, fractional excretion of uric acid, glucose, insulin and HOMA-IR for MFT and FMT at baseline and during cross-sex hormone therapy.

	MFT (n=22)	FMT (n=47)	p
BMI			
Baseline	22.2 (4.2)	25.4 (4.9)	<0.05
1 year	22.4 (3.7)	26.3 (4.2)**	<0.01
2 years	22.7 (4.9)	25.9 (4.3)	<0.05
Estradiol-17 beta			
Baseline	30.34 (17.21)	112.36 (71.80)	<0.001
1 year	42.34 (29.51)	65.19 (29.50)**	<0.01
2 years	56.75 (40.20)*	74.21 (47.42)**	NS
Total testosterone			
Baseline	5.81 (2.08)	0.51 (0.19)	<0.01
1 year	0.59 (0.89)**	8.20 (4.01)**	<0.001
2 years	0.34 (0.19)**	7.08 (3.82)**	<0.001
Serum uric acid			
Baseline	4.87 (1.19)	3.91 (0.85)	<0.001
1 year	3.67 (0.89)**	5.07 (0.93)**	<0.001
2 years	3.76 (1.13)**	5.02 (0.84)**	<0.001
FEUA	**n=19**	**n=25**	
Baseline	6.52 (2.15)	8.78 (2.62)	<0.01
2 years	8.90 (2.96)**	6.93 (2.47)**	<0.05
Glucose			
Baseline	93.60 (8.36)	88.65 (5.90)	<0.05
1 year	87.60 (8.46)	87.68 (6.23)	NS
2 years	86.50 (6.13)	87.35 (6.89)	NS
Insulin			
Baseline	13.08 (6.43)	10.71 (8.05)	NS
1 year	15.00 (4.24)	8.04 (4.65)**	<0.001
2 years	13.70 (5.23)	7.56 (4.17)**	<0.001
HOMA-IR			
Baseline	3.40 (1.76)	2.38 (1.71)	<0.05
1 year	3.29 (1.42)	1.80 (1.15)*	<0.01
2 years	2.86 (1.17)	1.79 (1.16)*	<0.01

Mean (SE). *p<0.05 compared with baseline. ** p<0.01 compared with baseline. NS: not significant.

Estradiol-17 beta (pg/mL), total testosterone (ng/mL), serum uric acid (mg/dL), FEUA (fractional excretion of uric acid, in percentage), glucose (mg/dL), insulin (μU/mL), and HOMA-IR (mmol/L x μU/mL).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Low dose
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Serum uric acid (mg/dl)
FEUA (%)