Effect of Long-Term Administration of Cross-Sex Hormone Therapy on Serum and Urinary Uric Acid in Transsexual Persons

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

Design: This was 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 (MFTs) and 47 female-to-male transsexuals (FMTs). The subjects were studied at baseline and 1 and 2 yr after starting cross-sex hormone treatment.

Results: The baseline levels of uric acid were higher in the MFT group. Compared with baseline, uric acid levels had fallen significantly after 1 yr of hormone therapy in the MFT group and had risen significantly in the FMT group. The baseline FEUA was greater in the FMT group. After 2 yr of cross-sex hormone therapy, the FEUA had increased in MFTs ($P = 0.001$) and fallen in FMTs ($P = 0.004$). In MFTs, the levels of uric acid at 2 yr 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 2 yr was associated with both the estrogen dose ($P = 0.02$) and the serum levels of estradiol-17β ($P = 0.03$). In MFTs, a correlation was found after 2 yr of therapy between the homeostasis model assessment of insulin resistance 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. (***J Clin Endocrinol Metab* 93: 2230–2233, 2008**)

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), although suggestions include the higher levels of estradiol (4–5) and a lower postsecretory tubular reabsorption of urate in women (6). Other studies defend the direct influence of insulin in the renal management of uric acid (7–10). Because 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 male-to-female transsexuals (MFTs) and female-to-male transsexuals (FMTs) undergoing cross-sex hormone therapy.

Subjects and Methods

The study involved a cohort of 69 healthy transsexuals (22 MFTs and 47 FMTs), selected consecutively, provided they fulfilled the diagnostic criteria of the Standards of Care of the World Professional Association for Transgender Health (11), had not previously received cross-sex hormone treatment, and had no known metabolic or inflammatory disease. The

Abbreviations: BMI, Body mass index; FEUA, fractional excretion of uric acid; FMT, female-to-male transsexual; HOMA-IR, homeostasis model assessment of insulin resistance; HRT, hormone replacement therapy; MFT, male-to-female transsexual.

0021-972X/08/$15.00/0

Printed in U.S.A.

doi: 10.1210/jc.2007-2467 Received November 6, 2007. Accepted March 11, 2008.

First Published Online March 18, 2008

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, the subjects started hormone therapy with a minimum 2-yr medical follow-up. The mean age of the MFTs was 23.1 ± 9.4 yr and the FMTs, 25.7 ± 6.0 yr. Of the MFTs, 18 had received conjugated oral estrogens, one oral estradiol valerate, and three transdermal estradiol patches. The daily estrogen dosage in the MFTs 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 hormone replacement therapy (HRT), medium dose twice that of HRT, and high dose more than twice that of HRT (12–14). The number of MFTs during the first year on low, medium, or high doses of estrogens was 16, six, and none, respectively, and during the second year, it was 13, four, and four, respectively. All the MFTs also received cyproterone acetate (50–100 mg/d).

In the FMTs, during the first year, 93.3% received 250 mg im testosterone enanthate or propionate each 2 wk, and 6.7% had 5 mg/d testosterone in patches. During the second year, 69.6% received injectable testosterone enanthate or propionate and 30.5% received testosterone in patches or gel.

The main variables were analyzed at each of the three study phases (baseline, 1 yr, and 2 yr after starting therapy). The anthropometric variables studied included weight and height [to calculate the body mass index (BMI; kilograms per square meter)]. The patients followed their usual diets throughout the study.

At each of the three study points, a fasting blood sample was obtained between 0800 and 1000 h and at least 12 h after the last dose of estrogens in the MFTs and 7 d after the parenteral administration of testosterone in the FMTs. After separating the serum, the samples were analyzed immediately. Serum measurements included total testosterone and estradiol-17β (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 homeostasis model assessment of insulin resistance (HOMA-IR).

Measurements were made in a subgroup of the transsexuals (19 MFTs and 25 FMTs) of uric acid and creatinine concentrations in 24-h urine samples (colorimetric enzymatic method). The FEUA (percent) was calculated at baseline and 2 yr 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 (milligrams per deciliter), CREAs is the creatinine in serum (milligrams per deciliter), UAs is the uric acid in serum (milligrams per deciliter), and CREAu is the creatinine in urine (milligrams per deciliter).

The statistical analysis was done with SPSS 11.5 for Windows (SPSS Inc., Chicago, IL). The quantitative variables are presented as means and SDs and the qualitative variables as proportions. The hypothesis contrast was made with the Student *t* 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 FMTs had a significantly greater BMI than the MFTs at all three study points. The BMI in the MFTs remained unchanged throughout the study. In the FMTs it increased significantly during the first year and remained stable during the second year (Table 1).

As expected, the baseline levels of estradiol-17β were significantly higher in the FMTs but fell during the first and second years of androgen treatment. At the same time, a significant increase was seen in testosterone levels. The MFTs showed a significant increase in levels of estradiol-17β 1 yr after starting estrogen therapy, and a very significant decrease in testosterone levels, with similar levels after 2 yr (Table 1).

The baseline levels of uric acid were significantly higher in the MFTs (Table 1). One year after starting treatment, the uric acid levels fell significantly in the MFTs and increased significantly in the FMTs. The uric acid levels differed significantly between the MFTs and FMTs after both 1 and 2 yr.

The baseline FEUA was significantly greater in the FMTs (Table 1). Two years after starting therapy, the FEUA had increased in the MFTs ($P = 0.001$) and fallen in the FMTs ($P = 0.004$). At this point, the FEUA levels were significantly greater in the MFTs than the FMTs (Table 1).

The levels of estradiol-17β 1 yr after starting treatment were higher in the MFTs 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 MFTs, showing no significant changes over the study period. The baseline levels of insulin were no different between the two groups. However, 1 yr after starting therapy, these levels fell significantly in the FMTs, remaining similar at the 2-yr point. Significant differences were found between the MFT and FMT groups after both 1 and 2 yr (Table 1).

The HOMA-IR was significantly greater in the MFTs at all three study points. Compared with the baseline levels, the HOMA-IR fell significantly after 1 yr in the FMTs but not the MFTs, remaining similar after 2 yr (Table 1). One year after starting therapy, the serum levels of testosterone in the FMTs correlated with the testosterone dose received ($r = 0.41$; $P = 0.004$).

In the MFTs, the levels of uric acid after 2 yr 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-17β correlated positively with FEUA in the MFTs ($r = 0.54$; $P = 0.04$). This correlation was absent in the FMTs.

In the MFTs, an ANOVA model showed that the FEUA at 2 yr was associated with both the dose of estrogens ($P = 0.02$) and the serum levels of estradiol-17β ($P = 0.03$).

In the MFTs, after 1 yr, serum levels of estradiol-17β correlated with the HOMA-IR ($r = -0.49$, $P = 0.03$). After 2 yr, 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

TABLE 1. BMI, serum levels of estradiol-17β, total testosterone, and uric acid and fractional excretion of uric acid, glucose, insulin, and HOMA-IR for MFTs and FMTs at baseline and during cross-sex hormone therapy

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

Mean (SE.). Following are measures used: estradiol-17β, picograms per milliliter; total testosterone, nanograms per milliliter; serum uric acid milligrams per deciliter; FEUA, percentage; glucose, milligrams per deciliter; insulin, microunits per milliliter; and HOMA-IR, millimoles per liter × microunits per milliliter. NS, Not significant.

[a] $P < 0.01$, compared with baseline.

[b] $P < 0.05$, compared with baseline.

cross-sex hormone therapy in persons with gender dysphoria and in an estrogen dose-dependent manner in MFTs.

Nicholls *et al.* (4) studied 22 MFTs before and 10 wk after treatment with stilbestrol or ethynylestradiol. They found a reduction in plasma levels of uric acid and an increase in renal clearance and FEUA. 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-17β, required to explain the effect of the estrogens on uric acid metabolism.

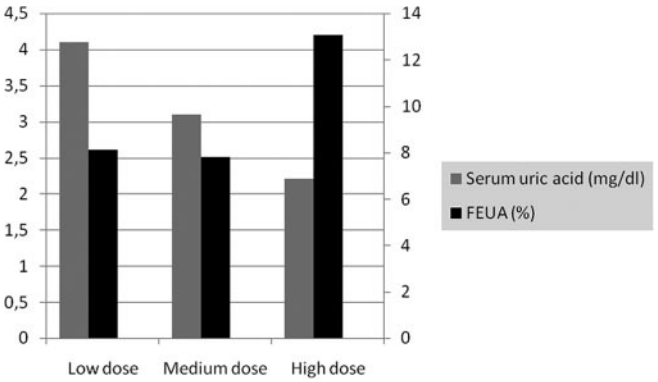

FIG. 1. Serum levels of uric acid and FEUA in relation with estrogen dose in MFTs after 2 yr of treatment ($P = 0.03$ for uric acid; $P = 0.04$ for FEUA).

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

The increased estrogen might improve insulin sensitivity resulting in increased FEUA and decreased serum uric acid. Some studies, although not all, have found that estrogens increase peripheral insulin sensitivity (10, 16). General population studies with a normal oral glucose tolerance test have found higher baseline levels of glycemia, uric acid, and HOMA-IR in men (17), whereas after an oral glucose tolerance test in women, an association was found between serum uric acid levels, insulin, and HOMA-IR (9). Polderman *et al.* (18) examined insulin sensitivity using a hyperinsulinemic-euglycemic clamp in 13 FMTs and 18 MFTs before and after 4 months of cross-sex hormone therapy; both groups showed a slight but significant reduction in insulin sensitivity after treatment. However, another more recent study involving 20 MFTs and 17 FMTs found that, after 1 yr of cross-sex hormone therapy, insulin sensitivity was

altered only in the MFT group (19). In our study, despite finding a weak statistical correlation between levels of estradiol-17β and HOMA-IR after 1 yr treatment, the transsexuals treated with estrogens experienced no change in their HOMA-IR or 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 FMTs 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 im enanthate or propionate. Another possibility is that the reduction in estrogens after cross-sex hormone therapy induces a decrease in FEUA and an increase in serum uric acid. Several authors have examined the influence of testosterone on uric acid levels, although the presence of such an association is still controversial (20, 21). The FMT group experienced a significant fall in HOMA-IR after 1 yr 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 coronary heart disease 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 MFTs. Additionally, the fact that FMTs 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.

Acknowledgments

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This work was partly supported by a grant from the Andalusian Health Service (SAS 0060/2006). This team belongs to the CIBER of Physiopathology of Obesity and Nutrition (CB06/03/0018), RETICS of Diabetes and Metabolism (RD06/0015/0008), and CIBERDEM CB07/08/0019 of the Instituto de Salud Carlos III, Spain.

Disclosure Statement: The authors have nothing to declare.

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