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Breast Tissues in Transsexual Women–A Nonprostatic Source of Androgen Up-Regulated Production of Prostate-Specific Antigen

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ABSTRACT

The present study made use of the female transsexual model and sought to evaluate the contributions of the ovarian, endometrial, and breast tissues to the androgen up-regulated production of prostate specific antigen (PSA). Serum levels of PSA were significantly raised in female transsexuals before surgery, after long-term androgen therapy (mean ± SE = 35.3 ± 6.2 pg/mL) when compared with female transsexuals before surgery, but with no androgen therapy (mean ± SE = 1.53 ± 0.25 pg/mL). In addition, in androngenized female transsexuals, after surgery, concentrations of PSA (mean ± SE = 14.5 ± 2.8 pg/mL) were significantly lowered compared with androngenized female transsexuals after surgery, but the levels were, nevertheless, significantly higher than in normal females. Monthly im injection of 250 mg Sustanon-250 to female transsexuals had raised serum testosterone levels to within the male range. In five subjects, in whom serial measurements were taken, serum testosterone levels were greatly raised 24 h after the testosterone therapy; the mean level (±SE) was 19.5 ± 2.1 ng/mL. But in spite of these high testosterone levels, serum PSA levels (mean ± SE = 2.2 ± 0.9 pg/mL) were not significantly raised. However, after 12 months of androgen therapy, the mean (±SE) PSA level in these five subjects was 47 ± 11.6 pg/mL and was significantly higher than the mean level in nonandrogenized female transsexuals. The present study confirmed that high levels of testosterone were able to up-regulate PSA production in women. This up-regulation of PSA production is both a dose- and time-dependent process. Furthermore, the evidence indicates that breast tissues are possibly a nonprostatic source of androgen up-regulated production of PSA women. (*J Clin Endocrinol Metab* **84:** 3313–3315, 1999)

RECENT studies have shown that prostate-specific antigen (PSA) is found in several nonserum tissue fluids and could be produced by several female tissues, including those of the breast, ovaries, and endometrium (1–3). As in men, it is believed that the production of PSA in females is up-regulated by androgens (4–6). Studies have also linked the regulation of PSA to different phases of the menstrual cycle, especially to the peak progesterone release during the luteal phase (7, 8). However, the precise nature of androgen up-regulation of PSA in females remains unclear (1, 9).

The present study evaluated the effects of the acute and chronic exposure to high levels of testosterone on the production of PSA in female transsexuals before and after their sex change surgery. The use of the transsexual model enabled us to assess the direct effect of high levels of testosterone on PSA production as well the relative contributions of the ovarian, endometrial, and breast tissues to serum PSA levels.

Materials and Methods

Informed consent was obtained from two groups of female transsexuals. A random blood sample was collected from each subject of the two groups. Group I comprised 48 female transsexuals who had yet to go through their sex change operation. It was further subdivided into two groups, Ia (pretreatment) and Ib (androngenized). Group Ia included the 32 individuals who had not been on any androgen therapy previously, while Group Ib included those 16 who had undergone androgen therapy (250 mg Sustanon-250/monthly) for between 4 and 48 months, according to previously reported hormone replacement regimes (10). Included in Groups Ia and Ib were 5 presurgery female transsexuals who were monitored longitudinally. Serum samples were collected before, 24 h after the first im injection of 250 mg Sustanon-250, and 12 months after the initiation of androgen therapy.

Group II (postsurgical) consisted of 15 female transsexuals who had undergone sex change operations that included reduction mammoplasty, castration, total hysterectomy, and the construction of a neophallus (11). They were on testosterone therapy (Sustanon-250, 250 mg/month) for between 5 and 72 months after their sex change surgery. Sustanon-250 (Organon, Scotland, UK) is a depot preparation consisting of a mixture of testosterone esters: testosterone propionate (30 mg), testosterone phenylpropionate (60 mg), testosterone isocaproate (60 mg), and testosterone deconoate (100 mg).

Serum PSA levels were measured using the ultrasensitive assay kits from DSL (Webster, TX). The minimum detection dose was 2 pg/mL. The interassay coefficients of variation calculated from several sets of the two internal quality control pools were less than 10%. The sum of the free and the antichymotrypsin (ACT)-bound fractions constituted the total immunoreactive PSA (12), and the kits measured the ACT-bound and free forms of PSA in equimolar concentrations. Serum levels that were lower than the detection limit of the assay were assigned a value of 1 pg/mL for statistical computations.

Serum testosterone concentrations were measured using both reagents and method from the World Health Organization Matched Reagent Program (13). The intra- and interassay coefficients of variation were less than 10%.

The one-way analysis of variances or the nonparamatric Kruskall Wallis test and paired *t* test were used for statistical analyses where appropriate.

Results

Serum levels of PSA were significantly raised ($P < 0.0001$) in androngenized female transsexuals (Group Ib) when compared with presurgical, pretreatment female transsexuals (Group Ia; Table 1). In addition, after the sex change operation, which included the total removal of the ovaries and the

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TABLE 1. Serum PSA and testosterone concentrations in the three groups of female transsexuals

Groups	PSA concentration (pg/mL) Mean ± SE	Median	Range	Mean testosterone levels (±SE) ng/mL
Pretreatment (Ia)	1.53 ± 0.25	1[a]	1–6	0.59 ± 0.04[b]
Androgenized (Ib)	35.3 ± 6.2	26[c]	13–96	6.2 ± 1.4
Postsurgical (II)	14.5 ± 2.8	11	2–35	10.0 ± 2.1

[a] Value is significantly lower than corresponding values in Groups Ib and II (nonparamatric test, Kruskall Wallis test, $P < 0.0001$);
[b] Value is significantly lower than corresponding values in Groups Ib and II (One-way ANOVA, $P < 0.0001$).
[c] Value is significantly higher than corresponding value in Group II ($P < 0.005$, Kruskall Wallis test).

womb and most of the breast tissues, the androgen up-regulation of PSA production was still evident. But serum levels of PSA were significantly lower when compared with corresponding levels in pre-operated androngenized female transsexuals of Group Ib (Table 1).

The monthly injection of 250 mg of Sustanon-250 (Organon) in female transsexuals before (Group Ib) and after (Group II) their sex change operation had raised serum testosterone levels to within the male range (2.5–9.7 ng/mL, 14) (Table 1). The levels of testosterone after the androgen therapy were not significantly different between Group Ib and Group II (Table 1).

In the five subjects in whom serial measurements were taken, serum testosterone levels were greatly raised 24 h after the im injection of 250 mg Sustanon; the mean level (±SE) was 19.5 ± 2.1 ng/mL and was significantly higher than corresponding levels in Group Ib. In spite of these high testosterone levels, serum PSA levels (mean ± SE = 2.2 ± 0.9 pg/mL), 24 h after the im injection of 250 mg Sustanon were not raised and were not significantly different from corresponding levels in subjects of Group Ia. However, after 12 months of androgen therapy, the mean (±SE) PSA levels in these five subjects was 47 ± 11.6 pg/mL and was significantly higher ($P = 0.018$; paired t-test) than their corresponding pretestosterone therapy levels (Fig. 1).

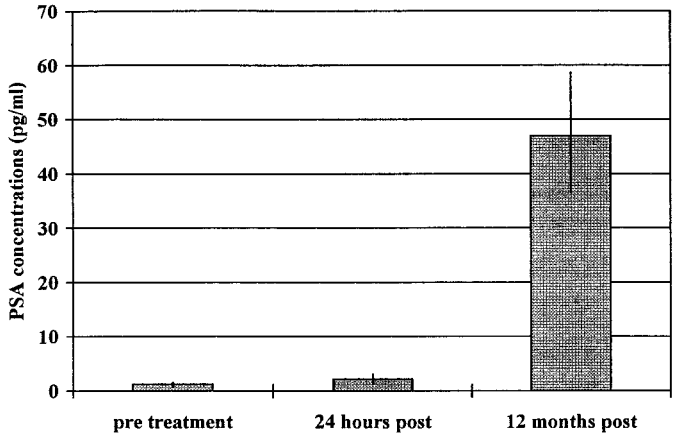

FIG. 1. Mean (±SE) PSA concentrations in five presurgical subjects before androgen treatment (pretreatment), 24 h after an im injection of 250 mg Sustanon (24 h post), and 12 months after androgen therapy, 250 mg Sustanon, monthly (12 months post).

Discussion

The use of female transsexuals in the present study enabled us to examine the direct effects of high levels of testosterone on the production of PSA in women. The results confirmed that PSA production in women could be up-regulated by exposure to raised testosterone levels as was suggested by earlier workers (1, 9, 15). Furthermore, the up-regulation is not just dose- but also time-dependent. Female transsexuals injected with 250 mg Sustanon 24 h previously, which raised serum levels of testosterone to more than double those found in normal men, did not show raised levels of PSA. Those five subjects monitored longitudinally, as well as the subjects exposed to long-term high androgen levels in Group Ib, had significantly raised PSA levels. It must be noted that blood samples from androngenized presurigical (Groups Ib) and postsurgical (Group II) female transsexuals were randomly collected without reference to the time when the last im injection of testosterone was administered. The wide scatter of testosterone levels noted in these subjects could be accounted for, in part, by the known uneven releases of testosterone from the depot preparation over the 4-week intervals. It is important to note that the current concentration of testosterone was not an index of its effect. More importantly, it was the duration and dose of the historical exposure that mattered (16). Therefore, these observations suggested that exposure to high levels of testosterone for a sufficiently long duration was required to up-regulate PSA production in women.

The androgen-induced increases in serum levels of PSA in female transsexuals after the total removal of the ovaries and the womb and partial removal of breast tissues were still significantly higher than corresponding levels in pretreatment female transsexuals, although they were significantly lower than in presurigical androngenized female transsexuals. These results implied that the remnant breast tissues left behind after the sex-change operation, including the nipples, were capable of producing significant amounts of PSA. Therefore, breast tissues are possibly a nonprostatic source for testosterone up-regulated production of PSA in women. This suggestion is supported by an earlier study, which showed that the ovaries and the adrenal are unlikely sources of PSA (9). In contrast to our study, Breul *et al.* (15) found significant differences in urinary levels of PSA, but not serum PSA between androngenized postsurgery female transsexuals and 20 females not treated with testosterone. This discrepancy with our results probably relates to the fact that the ability to up-regulate PSA production would depend upon the residual amount of breast tissues left after reduction mammoplasty.

However, the clinical significance of these findings is not clear in the present study, although several recent studies have implicated the usefulness of the measurement of PSA in management of women with breast cancer (17, 18).

In conclusion, the present study confirmed that high levels of testosterone are able to up-regulate PSA production in women. This up-regulation of PSA production in women is both a dose- and time-dependent process. Furthermore, the evidence indicates that breast tissues are possibly a nonprostatic source of androgen up-regulation of PSA production in women.

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