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 androgenized female transsexuals, after surgery, concentrations of PSA (mean ± SE = 14.5 ± 2.8 pg/mL) were significantly lowered compared with androgenized female transsexuals after surgery, but the levels were, nevertheless, significantly higher than in normal females. Monthly intramuscular 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 (±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 nonsemen 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 (androgenized). 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 regimens (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 intramuscular 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 mammaplasty, 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 nonparametric 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 androgenized 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
In conclusion, the present study confirmed that high levels 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 presurgical androgenized 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 androgenized 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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References