RAPID COMMUNICATION

# Prostate-specific antigen is increased in female patients with Cushing's disease

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**ABSTRACT. Prostate-specific antigen (PSA) is a serine protease with chymotripsine-like enzymatic activity, produced primarily by the prostate gland. It is widely used as a marker of androgen sensitive-prostate cancer. Likewise, women with androgen-dependent hirsutism have increased serum PSA levels. The aim of the present study was to investigate whether female patients with Cushing's disease had increased serum PSA concentrations. We studied 22 patients with active Cushing's disease. Twelve out of 22 patients were also evaluated after remission of the disease. Forty normal women with no signs of hirsutism served as controls. Mean serum PSA levels were higher in patients with active Cushing's disease than controls ($p$=0.005). Mean serum PSA levels decreased after remission of the disease (33.7±63.3 pg/ml *vs* 2.2±3.0 pg/ml, $p$<0.002, in active and cured patients, respectively). All patients with high serum PSA levels had a normalization of this parameter after the disease was cured. Serum T, DHEAS and $\Delta^4$ concentrations decreased after the remission of Cushing's disease. A positive correlation was found between serum PSA and T values (r=0.6, $p$<0.05). In conclusion, elevated serum PSA values are markers of androgen activity in female with Cushing's disease and their normalization may represent an additional index of remission of the disease.**

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## *INTRODUCTION*

Prostate-specific antigen (PSA) is a 33-kDa serine protease with chymotrypsin-like enzymatic activity (1). PSA is produced primarily by the prostate gland and is detectable in serum and seminal plasma; in addition, PSA is a specific serum marker for the diagnosis and follow-up of prostate cancer (2). Recently, the development of an ultrasensitive assay has allowed the detection of serum total PSA in a significant number of females with hirsutism (3-6), indicating that this protein may be a marker of hyperandrogenism. Further studies have reported the expression of PSA in various female tissues and fluids, such as breast, ovary, endometrium, milk, amniotic and breast cyst fluid (7). PSA gene expression and protein production appear to be up-regulated by androgens, glucocorticoids and progestins (8, 9). Since, a significant proportion of female patients with Cushing's syndrome presents signs of hyperandrogenism (acne, amenorrhoea and hirsutism), the aim of the present study was to evaluate whether female patients with Cushing's disease have increased serum total PSA levels.

## *SUBJECTS AND METHODS*

### *Subjects*

Twenty-two women with active ACTH-dependent Cushing's disease (mean age ±SD 40±11 yr, range 18-59 yr) were enrolled in the study. A longitudinal study was conducted in 12 (mean age 40±14 yr, range 18-59 yr) patients out of 22 (CD Long); these patients were evaluated during the activity of disease (CD-Act,) and in remission (CD-Rem) 1-3 yr after transsphenoidal adenomectomy (no.=9) or with the addition of radiotherapy and bilateral adrenalectomy (no.=3). Forty normal women (mean age 40±13 yr, range 17-66 yr) matched for age and with no signs of hirsutism served as controls (Controls). Neither the patients nor controls had taken contraceptive pills or transdermal estrogen during the study period. Diagnosis of Cushing's disease and the definition of remission were based on standard clinical and laboratory criteria (10).

**Key-words:** PSA, Cushing, cortisol, hyperandrogenism, T, DHEAS, $\Delta^4$.

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### *Assays*

Serum total PSA was measured by an ultrasensitive chemiluminescent enzyme immunoassay (Immulite Third Generation PSA, Diagnostic Products Corp., Los Angeles, CA, USA) with a sensitivity of 3 pg/ml. All serum samples were analyzed in duplicate in a single run; the intra-assay coefficient of variation was <10%. Commercial kits were used for serum T (n.v. 0.1-1.0 ng/ml) (DiaSorin, Saluggia, Italy), DHEAS (n.v. 350-4300 ng/ml) (Immulite, Diagnostic Products Corp., Los Angeles, CA, USA), $\triangle^4$ (n.v. 0.4-3.0 ng/ml) (DiaSorin Inc., Stillwater, MN, USA), cortisol (n.v. 85-250 ng/ml) (Immunotech, Marseille, France) and ACTH (n.v. 9-52 pg/ml) (Nichols Institute Diagn., San Juan Capistrano, CA, USA) measurements.

### *Statistical analysis*

Baseline values were expressed as mean±SD; unpaired and paired *t* test and linear regression analysis were used as appropriate; some analyses were performed after log transformation.

## *RESULTS*

Mean serum total PSA concentrations were higher in CD than controls (26.4±47.4 pg/ml *vs* 4.8±4.2 pg/ml, $p$=0.005). Serum PSA levels ranged <3-14 pg/ml in Controls and <3-229 pg/ml in CD-Act. Ten out of 22 patients (45%) with CD had serum PSA values higher than 14 pg/ml.

In the CD-Long group mean serum PSA levels were higher in CD-Act than CD-Rem (33.7±63.3 *vs* 2.2±3.0 pg/ml, $p$<0.002). Serum PSA levels were higher than >14 pg/ml in 5/12 (42%) CD-Act patients and normalized after the cure of disease. The remaining 7 (58%) CD-Act patients had serum PSA levels into the normal range, which had a further decrease after remission of the disease (Fig. 1). After the remission a decrease in serum T (1.1±1.1 ng/ml vs 0.2±0.2 ng/ml, $p$<0.05), DHEAS (2833±2630 ng/ml *vs* 627±1052 ng/ml, $p$=0.01) and $\triangle^4$ (3.0±3.5 ng/ml *vs* 0.6±0.4 ng/ml, $p$=0.01) concentrations was observed.

A positive correlation in CD-Act and CD-Rem patients between serum PSA and >T levels was found (r=0.6, $p$<0.05 and r=0.9, $p$<0.0001, respectively) (Fig. 2) but not with $\triangle^4$ and DHEAS concentrations.

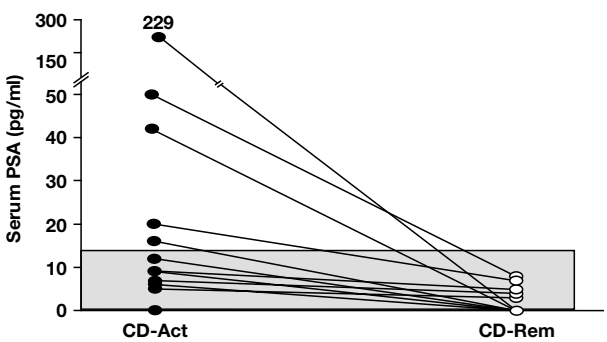


Fig. 1 - *Serum total PSA levels in patients with Cushing's disease before (CD-Act) and after the remission (CD-Rem). The shaded area represents the range obtained in 40 controls.*

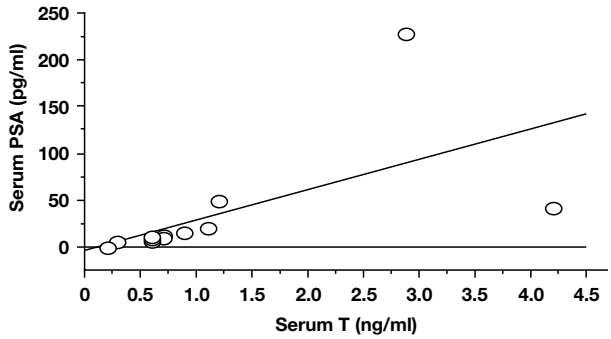


Fig. 2 - *Correlation between serum PSA and T concentrations in patients with active Cushing's disease (r=0.6,* p*<0.05).*

## *DISCUSSION*

With the development of a highly sensitive immunofluorometric total PSA assay, elevated serum PSA levels related with serum androgens concentrations have been reported in hirsute women (3-6). Subsequent studies identified this protein in many female tissues such as breast, ovary and endometrium (7).

The results of the present study showed that female patients with active Cushing's disease have increased serum PSA concentrations compared to controls, and that in half of them serum PSA values are above the normal range. PSA normalized after the cure of disease in all patients with high levels at baseline; in the other, with normal PSA values, a further decrease after remission of CD was observed. At the same time there was a reduction in serum T, DHEAS and $\triangle^4$ levels. Serum PSA concentrations were correlated with serum T levels both before and after remission of disease, accordingly with the data by Negri *et al.* who observed a concomitant reduction of serum PSA and androgens in hirsute women (5) after therapy. Furthermore, *in vitro* studies using a breast carcinoma cell line indicate that the production of PSA is under the control of steroid hormones, including androgens and progestins (9). The fact that PSA values are elevated in about 50% of the patients with CD and that are related to androgens and not to cortisol levels is in keeping with either the androgen-dependent regulation of PSA or to the fact that hyperandrogenism is not invariably present in all patients with CD.

In conclusion serum total PSA measurement could be considered a marker of androgen activity in female with Cushing's disease. In female patients with active Cushing's disease and elevated serum PSA concentrations the measurement of this protein may be considered an additional, useful parameter of the remission of disease. Further studies in a large population with Cushing's disease are necessary to confirm this data.

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