

NOTE

Effects of Gonadotropin and Testosterone Treatments on Prostate Volume and Serum Prostate Specific Antigen Levels in Male Hypogonadism

METIN OZATA, MERTOL BULUR, ZEYNEL BEYHAN, ALI SENGÜL*, MUTLU SAGLAM**, MUSTAFA TURAN, AHMET CORAKCI, AND M. ALI GUNDOGAN

Department of Endocrinology and *Metabolism, Immunology and **Radiology, Gülhane School of Medicine, Etlik-Ankara 06018, Turkey

Abstract. It is known that prostate specific antigen (PSA) is strongly androgen dependent, but little is known about the effects of gonadotropin and testosterone treatments on the prostate and serum PSA levels in male hypogonadism. We have therefore determined serum PSA levels before and 3 months after treatment in 13 patients with idiopathic hypogonadotropic hypogonadism (IHH) and 14 patients with Klinefelter's syndrome. Plasma FSH, LH, testosterone, PRL, testis and prostate volumes were also determined before and 3 months after treatments. Patients with IHH were treated with hCG/hMG and patients with Klinefelter's syndrome received testosterone treatment. PSA levels were determined by a kinetic enzyme immunoassay method. In patients with Klinefelter's syndrome FSH and LH levels were significantly decreased but total and free testosterone and PSA levels were significantly increased after 3 months of treatment. Right and left testicular volumes were not significantly changed whereas prostate volumes were significantly increased after treatment. In this group PSA levels were significantly and positively correlated with the prostate volume both before ($r=0.54$, $P=0.048$) and after treatment ($r=0.61$, $P=0.012$). In the IHH group total and free testosterone and PSA levels were significantly increased after gonadotropin treatment but FSH and LH levels did not change significantly. Right and left testicular volumes and the prostate volumes were also significantly increased after 3 months of gonadotropin treatment. In this group PSA levels were correlated with prostate volume before ($r=0.74$, $P=0.004$) treatment but not after therapy ($r=0.35$, $P=NS$). Our results show that serum PSA levels increase after gonadotropin and testosterone treatment in male hypogonadism, but this could not be used as an index for the evaluation of the androgen action in the treatment of male hypogonadism, since PSA levels following treatments were correlated with the prostate volume or T levels only in patients with Klinefelter's syndrome but not in the IHH group.

Key words: Prostate specific antigen (PSA), Male hypogonadism, Testosterone, Gonadotropin
(Endocrine Journal 44: 719–724, 1997)

PROSTATE-specific antigen (PSA) is a single chain glycoprotein with a mol weight of about 33 kilodaltons produced mainly by the prostate epithelium [1]. Recent studies demonstrated that

PSA is also produced by the periurethral and the perianal glands as well as the endometrial tissue and the normal breast after pregnancy [2–5]. But the amount of PSA produced in these tissues is much smaller than those produced by prostatic cells [6]. It is shown that PSA is a useful marker for the detection and follow-up of patients with prostatic carcinoma [1, 7]. Moreover, Diamantis *et al.* [6, 8] suggested that PSA is also a favorable prognostic marker in female breast cancer.

Received: February 26, 1997

Accepted: June 20, 1997

Correspondence to: Dr. Metin OZATA, Dept. of Endocrinology & Metabolism, Gülhane School of Medicine, Etlik-Ankara 06018, Turkey

It is known that PSA production is strongly androgen dependent. Vieira *et al.* [10] recently suggested that PSA measurement could be used as a marker for androgen action and pubertal development in normal boys, but a few studies evaluated the effect of androgen replacement therapy on prostate volume and serum PSA levels in male hypogonadism. Behre *et al.* [11] and recently Palapattu *et al.* [12] demonstrated that testosterone substitution therapy increases prostate volume and PSA levels only to a range comparable to that in age-matched normal men. Although effects of gonadotropin-releasing hormone treatment on prostate volume were evaluated in hypogonadotropic hypogonadism [13], no study reported the effect of gonadotropin treatment on the prostate and serum PSA levels in male hypogonadism.

We have therefore evaluated serum PSA levels before and after treatment in male hypogonadism to establish PSA measurement as a potential marker of androgen action in the treatment of male hypogonadism.

Patients and Methods

Patients

Thirteen untreated male patients with idiopathic hypogonadotropic hypogonadism (IHH) (mean age: 21.6 ± 0.77 years; range 21 to 23) and 14 male patients with primary hypogonadism (mean age: 21.4 ± 0.51 years, ranges 21 to 22) were included in this study. The diagnosis of IHH was based on severely retarded sexual maturation failure to undergo puberty spontaneously before 18 years of age and was confirmed by a decreased serum T concentration below the normal range for adults, FSH and LH levels within or below the normal range, the absence of a pituitary or hypothalamic mass lesion on computerized tomography or MRI, the presence of gonadotropin response to repetitive doses of gonadotropin-releasing hormone (GnRH), and normal smell test and normal karyotypes (46, XY). None of the patients had hyposmia or anosmia or a family history of IHH. All patients had scrotal testes with a mean (\pm SD) left (3.02 ± 1.72 cc) and right testicular volume (2.79 ± 1.69 cc).

Fourteen patients with primary hypogonadism

had Klinefelter's syndrome with XXY karyotypes. All patients with Klinefelter's syndrome had a low serum T concentration but high FSH and LH levels.

All hypogonadal men had normal baseline serum FT₄, TSH, PRL, GH and cortisol concentrations. Bone age was estimated by using the radiological method of Greulich *et al.* [14].

Therapy and analysis

Thirteen patients with IHH were treated with hCG (Profasi, Serono Laboratories Aubonne, Switzerland) 5000 IU, three times a week IM injection along with 1 vial hMG (Pergonal, Serono Laboratories, Aubonne, Switzerland; 75 IU FSH plus 75 IU LH/vial). Fourteen patients with Klinefelter's syndrome were treated with three weekly IM injections of Sustanon 250 (NV Organon, Oss, The Netherlands) which contained 30 mg T propionate, 60 mg T isocaproate and 100 mg T decanoate. Follow-up evaluations were performed 3 months later. Plasma FSH, LH, PRL, total T, free T and SHBG were measured the day before scheduled injections of hMG/hCG in the IHH group. In patients with Klinefelter's syndrome, blood was taken at the midpoint between Sustanon injections. Blood samples were drawn between 0700 and 0900 h to avoid any influence of the circadian testosterone rhythm and before the prostate ultrasound to avoid minor changes in serum PSA levels. Sera were stored at -20°C until PSA analysis. Clinical status and gonadotropin and sex-steroid levels were established during the initial diagnostic evaluation.

Clinical and biochemical data have been assessed 3 months after therapy in all patients. Testis and prostate volumes have been assessed by ultrasound before and 3 months after therapy. Prostate volumes are measured by transrectal ultrasonography. An Acuson 128 xp/10 instrument (Acuson Corporation, Mountain View, CA USA) was used in all cases for measurement of testis and prostate volumes as described previously [15, 16].

All patients were informed about the aim and the procedure of the study and gave their written consent. The study was approved by the local Ethical Committee of the Gülhane School of Medicine.

Hormone and PSA measurements

Serum FSH, LH, and PRL were measured by immunoradiometric assay (IRMA) with reagents from Radim Techland SA (Angleur, Belgium; FSH IRMA CT, LH IRMA CT and PRL IRMA CT kits, respectively). The detection limits for FSH, LH and PRL were 0.18 IU/L, 0.20 IU/L, and 1 µg/L, respectively. The intra and inter-assay coefficients of variation (CV) for FSH were 4.4 and 6.0%, for LH 4.8 and 5.4% and for PRL 4.6 and 6.0%, respectively. Serum free testosterone (FT) was determined by a solid-phase I¹²⁵ radioimmunoassay (RIA) with reagents from Diagnostic Product Corporation (Los Angeles, USA; Coat-A-Count free testosterone Kit). The detection limit for FT was 0.15 pg/mL. The intra and inter-assay CV for FT was 3.8 and 4.2%, respectively. Serum total testosterone (TT) was measured by RIA with reagents from Diagnostic Systems Laboratories Inc. (Webster, TX, USA; Active Testosterone Kit). The detection limit for TT was 0.1 ng/mL. The intra and interassay CVs for TT were 9.3 and 11.0%, respectively. Serum sex hormone-binding globulin (SHBG) was measured by RIA with reagents from Radim Techland SA (Angleur, Belgium; SHB GRIA I¹²⁵ Kit). The intra and interassay CV for SHBG was 3.6 and 7.9%, respectively. PSA levels were determined in the same assay by a kinetic enzymatic immunoassay (EIA) method with reagents from Diagnostic Product Corporation (Los Angeles, USA; Milenia, PSA Kit). Intra assay CV for PSA was 4.9%.

Statistical analysis

All results are given as means ± SD. Wilcoxon matched pairs signed rank test (Wilcoxon 2 test) was used to determine whether changes occurred in selected parameters with the treatment. Correlations between PSA and other parameters were calculated by Sperman's correlation test. $P < 0.05$ was considered statistically significant.

Results

Clinical and laboratory characteristics of 14 patients with Klinefelter's syndrome before and 3 months after testosterone treatment are shown in Table 1. FSH and LH levels were significantly decreased at 3 months after T therapy, but significant increases in total T, free T and PSA levels were observed. The prostate volume was also significantly increased after T therapy. Right and left testicular volumes were decreased. But these decreases were not statistically significant. SHBG levels had not changed significantly 3 months after therapy, although a trend toward a decrease was observed. In this group, no correlation was found between PSA levels and FSH, LH, SHGB, free T levels or testicular volumes both before and after treatment. PSA levels were significantly correlated with prostate volumes both before ($r=0.54$; $P=0.048$) and after treatment ($r=0.56$; $P=0.037$). In this group total testosterone levels were significantly correlated with PSA levels both before ($r=0.61$;

Table 1. Clinical and laboratory characteristics of 14 men with Klinefelter's syndrome treated with testosterone

Variable	Before treatment	After treatment	P*
FSH (IU/L)	48.06 ± 8.73	37.16 ± 9.05	0.0015
LH (IU/L)	25.12 ± 10.8	17.52 ± 5.57	0.0092
PRL (µg/L)	2.22 ± 0.32	2.62 ± 2.33	NS
Total testosterone (ng/mL)	0.79 ± 0.44	4.44 ± 4.59	0.0010
Free testosterone (pg/mL)	1.75 ± 0.88	19.09 ± 12.91	0.0010
Prostate specific antigen (ng/mL)	0.99 ± 0.14	1.10 ± 0.14	0.0117
Serum sex hormone-binding globulin (nmol/L)	46.25 ± 23.21	44.65 ± 28.53	NS
Right testis vol (cc)	1.14 ± 0.51	1.11 ± 0.48	NS
Left testis vol (cc)	1.16 ± 0.50	1.12 ± 0.42	NS
Prostate volume (cc)	4.30 ± 1.77	5.77 ± 2.26	0.0110

* Wilcoxon test.

Table 2. Clinical and laboratory characteristics of 13 men with IHH treated with hCG/hMG

Variable	Before treatment	After treatment	P*
FSH (IU/L)	0.96± 0.67	1.64 ± 2.52	NS
LH (IU/L)	1.01± 0.56	0.78 ± 0.55	NS
PRL (mg/L)	3.04± 2.62	3.32 ± 2.54	NS
Total testosterone (ng/mL)	0.62± 0.41	3.0 ± 2.08	0.0015
Free testosterone (pg/mL)	1.56± 1.67	15.33 ±14.32	0.0024
Prostate specific antigen (ng/mL)	1.00± 0.25	1.25 ± 0.22	0.0077
Serum sex hormone-binding globulin (nmol/L)	60.99±34.20	49.27 ± 25.32	NS
Right testis vol (cc)	2.79± 1.69	3.57 ± 2.11	0.0150
Left testis vol (cc)	3.02± 1.72	4.00 ± 1.80	0.0058
Prostate volume (cc)	3.77± 2.39	6.27 ± 2.73	0.0015

*Wilcoxon test.

$P=0.012$) and after treatment ($r=0.54$, $P=0.047$). No correlation was found between the prostate volume and FSH, LH, SHBG, free T levels, or testicular volumes both before and after treatment, but total testosterone levels were significantly correlated with the prostate volume before treatment ($r=0.61$, $P=0.019$) but not after treatment ($r=0.049$, $P=0.8$).

As shown in Table 2, FSH, LH and SHBG levels had not changed significantly at 3 months after hCG/hMG treatment in the IHH group. Mean total and free T, and PSA levels had risen significantly at 3 months after treatment. Right and left testicular volumes and prostate volumes were also significantly increased after treatment. In this group, no correlation was found between PSA levels and FSH, LH, total T, Free T or testicular volumes both before and after treatment, but SHBG levels were negatively and significantly correlated with PSA levels only before treatment ($r=-0.61$, $P=0.018$) but not after treatment ($r=0.33$, $P=0.26$). PSA levels were significantly and positively correlated with prostate volume before ($r=0.74$; $P=0.004$) but not after therapy ($r=0.35$, $P=0.2$). No correlation was found between the prostate volume and FSH, LH, TT, free T or right testicular volumes both before and after treatment. The prostate volume was significantly correlated with left testicular volume and SHBG both before ($r=0.61$, $P=0.025$; $r=-0.70$, $P=0.008$, respectively) and after treatment ($r=0.62$, $P=0.0024$; $r=-0.58$, $P=0.035$, respectively).

Discussion

The major finding of this study was that PSA levels in both Klinefelter's syndrome and IHH groups were significantly increased after treatment. PSA levels were correlated with prostate volumes only in the Klinefelter's syndrome group both before and after treatment, but not in the IHH group after treatment.

In agreement with previous studies, our results show that androgen replacement therapy increases the prostate volume in male hypogonadism [11, 13, 17]. Conversely, in patients with benign prostatic hyperplasia, treatment with a GnRH agonist resulted in suppression of serum testosterone levels and decreases in prostate volume [18, 19]. To our knowledge, PSA levels in male hypogonadism have only been reported by Behre *et al.* [11] in a controlled cross-sectional study, and no study reported the PSA levels before and after treatment in male hypogonadism. Our results show that PSA levels increase after both gonadotropin and testosterone treatment in accordance with the increases in prostate volume, but PSA levels did not demonstrate a relationship to prostate volume or T levels after treatment in the IHH group. Contrary to our findings, Behre *et al.* [11] found no correlation between PSA and the prostate volume in a group of untreated male patients consisting of primary and secondary hypogonadal patients, but the authors found a significant positive correlation between PSA and prostate volume in a group of hypogonadal patients (both primary and secondary

hypogonadals) who were treated with testosterone for longer than 6 months. The reason for this discrepancy between our study and Behre's is not clear. It is possible that the different etiology of male hypogonadism, sample size, assay sensitivity or duration of treatment may be the reason for this discrepancy. It is also possible to consider that the PSA production rate would also differ in each individual, because the human prostate is not of homogenous components. It would therefore be expected that serum PSA correlates with the prostate volume in some patients and not in others. Our results suggest that PSA levels could not be used as an index of androgen action in the treatment of male hypogonadism since its level was correlated with only in a subgroup of male hypogonadism after treatment. Wallace *et al.* [20], supporting this view, reported that supraphysiological serum testosterone levels after high-dose testosterone enanthate administration in healthy subjects did not result in changes in serum PSA levels. Although Behre *et al.* [11] showed that

effective testosterone treatment of hypogonadal men increases the prostate volume and PSA levels only to a range comparable to that in age-matched normal men, the long-term effect of gonadotropin therapy on PSA levels remains to be clarified.

Overall, our results show that short-term gonadotropin and testosterone treatment cause a significant increase in serum PSA levels in male hypogonadism, but this increase is correlated with the prostate volume or circulating T levels only in patients with Klinefelter's syndrome both before and after T treatment. Thus our results suggest that serum PSA levels could not be used as an index for the evaluation of androgen action in the treatment of male hypogonadism.

Acknowledgements

We are grateful to Aysel Pekel for laboratory assistance and Demir Sarman and Ehat Yenigun for typing the manuscript.

References

1. Armbruster DA (1993) Prostate-specific antigen: Biochemistry, analytical methods, and clinical application. *Clin Chem* 39: 181–195.
2. Kamoshida S, Tsutsumi Y (1990) Extraprostatic localization of prostate specific antigen: Distribution in cloacogenic glandular epithelium and sex-dependent expression in human anal gland. *Hum Pathol* 21: 1108–1111.
3. Frazer HA, Humphrey PA, Burchette JL, Paulson DF (1992) Immunoreactive prostatic specific antigen in male periurethral glands. *J Urol* 147: 246–248.
4. Clements A, Mukhtar A (1994) Glandular kallikreins and prostate specific antigen are expressed in the human endometrium. *J Clin Endocrinol Metab* 78: 1536–1539.
5. Yu H, Diamandis EP (1995) Prostate specific antigen in milk of lactating women. *Clin Chem* 41: 54–60.
6. Diamandis EP, Yu H (1995) Editorial: New biological functions of prostate-specific antigen? *J Clin Endocrinol Metab* 80: 1515–1516.
7. Osterling JE (1991) Prostate specific antigen: A critical assessment of the most useful tumor marker for adenocarcinomas of the prostate. *J Urol* 145: 907–923.
8. Diamandis EP, Yu H, Sutherland DJA (1994) Detection of prostate specific antigen immunoreactivity in breast tumors. *Breast Cancer Res Treat* 32: 301–310.
9. Seamons B (1988) Reference intervals for prostate-specific antigen. *Clin Chem* 34: 1366–1367.
10. Vieira JGH, Nishida SK, Pereira AB, Arraes RF, Verreschi ITN (1994) Serum levels of prostate-specific antigen in normal boys throughout puberty. *J Clin Endocrinol Metab* 78: 1185–1187.
11. Behre HM, Bohmeyer J, Nieschlag E (1994) Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal control. *Clin Endocrinol* 40: 341–349.
12. Palapattu GS, Gollapudi GM (1996) Effect of testosterone substitution therapy on the prostate of hypogonadal men. Proceeding of the 10th International Congress of Endocrinology. Abstract No: P1–166.
13. Canale D, Andreini F, Mais V, Melis GB, Turchi P, Menchini-Fabris GF (1990) Ultrasound monitoring of testis and prostate maturation in hypogonadotropic hypogonadic males during gonadotropin-releasing hormone treatment. *Fertil Steril* 53: 537–540.
14. Gruelich WW, Pyle SI (1959) Radiographic Atlas of Skeletal Development of the Hand and Wrist. 2nd ed, Stanford: Stanford University Press.
15. Terris MK, McNeal TA (1992) Estimation of prostate cancer volume by transrectal ultrasound imaging.

- J Urol* 147: 855–857.
16. Littrup PJ, Williams CR, Egglin TK, Kane RA (1991) Determination of prostate volume with transrectal US for cancer screening. Part II. Accuracy of *in vitro* and *in vivo* techniques. *Radiology*. 179: 49–53.
 17. Bartsch G, Egender G, Hübscher H, Rohr H (1982) Sonometrics of the prostate. *J Urol* 127: 1119–1121.
 18. Gabrilove JL, Levine AC, Kirschenbaum A, Droller M (1989) Effect of long-acting gonadotrophin-releasing hormone analog (Leuprolide) therapy on prostatic size and symptoms in 15 men with prostatic hyperthyrophy. *J Clin Endocrinol Metab* 69: 629–632.
 19. Peters CA, Walsh PC (1987) The effect of nafarelin acetate, a luteinizing-hormone-releasing hormone agonist, on benign prostatic hyperplasia. *N Engl J Med* 317: 599–604.
 20. Wallace EM, Pye SD, Wild SR, Wu FCW (1993) Prostate specific antigen and prostate gland size in men receiving exogenous testosterone for male contraception. *Int J Androl* 16: 35–40.