Serum testosterone levels, testis volume, and the risk of prostate cancer: are these factors related?

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ABSTRACT

Objective: Inconclusive results have been published in the literature regarding the relationship between free and total serum testosterone levels and prostate cancer. We investigated the relationship between total and free serum testosterone levels, testes volume, and prostate cancer in our patient population.

Material and methods: Total and free serum testosterone levels and serum PSA levels were recorded for 102 consecutive patients. All of the patients underwent transrectal ultrasonography-guided prostate biopsy due to an abnormal digital rectal examination finding and/or a serum PSA level of >4.0 ng/mL. All of the transrectal and testis US examinations and prostate biopsies were performed by the same radiologist. The testis length, width, and height were measured from transverse and longitudinal gray scale images, and the testis volume was calculated.

Results: Prostate cancer was detected in 32 of 102 patients (31.3%) who underwent prostate biopsy (prostate cancer group). The remaining patients had benign histopathological findings (prostate cancer-free group). The prostate cancer and benign histology groups were compared for age, total and free testosterone, PSA values, and testis volume. The patients with prostate cancer were found to have a higher mean age ($p=0.04$). There were no significant differences in serum PSA levels, free or total testosterone levels, or testis volumes between the two groups ($p>0.05$). A binary logistic regression analysis showed that neither free nor total testosterone was a predictor of prostate cancer ($p=0.315$ and $p=0.213$, respectively). Only age was found to be a significant risk factor for the development of prostate cancer ($p=0.02$).

Conclusion: Our study failed to show a relationship between total or free serum testosterone levels, testis volume, and the risk of prostate cancer. Therefore, monitoring serum testosterone levels for prostate cancer prediction does not appear to add an advantage over PSA screening.

Key words: Prostate cancer; PSA; testis; testosterone.

Introduction

Prostate cancer is one of the major problems facing men and is of great interest to urologists. Family history, age, and race are among the risk factors for prostate cancer. Androgens are known to affect the growth rate and progression of prostate cancer, but it is not clear whether elevated or decreased concentrations of serum testosterone increase the risk of prostate cancer development.^[1] It is known that sex steroid hormones are essential for the growth of normal prostate tissue and that they play a role in the proper differentiation of prostate epithelium.^[2] In addition, the prostate gland is important in androgen metabolism because it is the site where testosterone is irreversibly convert-

ed to 5 α -dihydrotestosterone by the enzyme 5 α -reductase type II.^[3] There is a hypothesis that the androgenic activity within the prostate gland is not reflected by serum testosterone levels, and it is largely related to the concentration of 5 α -dihydrotestosterone within the glandular tissue. Therefore, serum testosterone levels may not help to estimate the risk of prostate cancer development.^[4] Inconclusive results have been published in the literature concerning the relationship between the free and total serum testosterone levels and prostate cancer. Some investigators have found no relationship between serum testosterone levels and prostate cancer development.^[5] In contrast, it has also been suggested that free serum testosterone levels are associated with an increased risk of prostate cancer.^[6]

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Submitted:
05.06.2012

Accepted:
14.08.2012

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Androgen ablation therapy is frequently used in prostate cancer management because it has been shown that a significant reduction in serum testosterone levels results in regression of advanced prostate cancer.^[7] Decreasing testosterone to castration levels causes prostate cancer regression, but there has been no conclusion regarding whether the serum hormone levels affect the aggressiveness of prostate cancer.^[5] It has also been clearly demonstrated that biochemical androgen deficiency increases with age and that testosterone treatment is contraindicated if there is a known or suspected prostate cancer.^[8]

The aim of this study was to investigate the relationship between total and free serum testosterone levels, testis volume, and prostate cancer in our patient population.

Material and methods

Total and free serum testosterone levels and serum PSA values were recorded in 102 patients with lower urinary tract symptoms who were admitted to our department between April 2007 and November 2009. Patients with a family history of prostate cancer or who had previously undergone hormone therapy for hypogonadotrophic hypogonadism, or hypergonadotrophic gonadism or prior prostate surgery were excluded. All of the patients underwent transrectal ultrasonography-guided prostate biopsy due to an abnormal digital rectal examination finding and/or serum PSA level >4.0 ng/mL. Written informed consent was obtained from all of the patients.

All US examinations and biopsies were performed by the same radiologist who has worked in our department for 10 years. An SSA 250A Toshiba US system (Toshiba, Tokyo, Japan) with a 3.5 MHz sector transducer was used. Biopsy specimens were obtained using in our department for 10 years. The number of cores taken in every procedure was 12-14 cores. None of the patients had been previously diagnosed with or treated for prostate or testis cancer, and none of the patients had received hormone therapy.

Testis ultrasound was performed by the same radiologist using an 8-MHz transducer. The testis length, width, and height were measured from transverse and longitudinal gray scale images. The testis volume was calculated using the formula length x width x height x 0.71.

The two groups of patients (with and without prostate cancer) were compared using the chi-squared test and Fisher's exact test for qualitative variables, and the Mann-Whitney U test was used to compare quantitative variables. The Kolmogorov-Smirnov analysis was used to test for normal distributions. For multivariate analysis, a binary logistic regression analysis with

the forward stepwise method was performed. A p value of 0.05 was accepted as the level of statistical significance.

The results are expressed as the mean $\pm$ standard deviation (SD).

Results

Prostate cancer was detected in 32 of 102 patients (31.3%) who underwent prostate biopsy (patients with prostate cancer group). The rest of the patients had benign histopathological findings, including prostatitis and benign prostatic hyperplasia (patients without prostate cancer group). The prostate cancer and benign histology groups were compared for age, total and free serum testosterone levels, PSA levels, and testis volume. The mean age was 64.9 ± 6.4 years in patients with prostate cancer and 60.9 ± 6.2 in patients without prostate cancer. The mean serum PSA level was 7.5 ± 0.7 ng/mL in patients with prostate cancer and 7.1 ± 2.5 ng/mL in patients without prostate cancer. The mean levels of free testosterone in patients with or without prostate cancer were 9.1 ± 4.3 ng/dL and 11.1 ± 8.6 , respectively. The mean levels of total testosterone in patients with or without prostate cancer were 484.6 ± 200.8 and 459.2 ± 132.5 , respectively. The mean testis volumes were 21.25 ± 4.65 cc in patients with prostate cancer and 20.68 ± 5.32 cc in patients without prostate cancer.

The patients in the prostate cancer group were found to have a higher mean age ($p=0.04$). There were no significant differences in serum PSA levels, free or total serum testosterone levels, or testis volume between the patient groups ($p>0.05$).

These results are summarized in Table 1.

A binary logistic regression analysis showed that neither free nor total testosterone was a predictor of prostate cancer ($p=0.315$ and $p=0.213$, respectively). Only age was found to be a significant factor for the development of prostate cancer ($p=0.02$).

These results are summarized in Table 2.

Discussion

We could not find an association between total or free serum testosterone levels, testis volume, and prostate cancer. The only risk factor we could confirm was patient's age. Our findings are consistent with a collaborative study of endogenous hormones and prostate cancer in which no relationship was found between any serum sex hormone level and the development of prostate cancer. The authors only reported an inverse association between serum sex hormone binding globulin (SHBG) concentration and prostate cancer risk.^[9] In a recent study by Morote

et al.^[5], in addition to failing to show a relationship between testosterone levels and prostate cancer, the authors could not find a relationship between the serum levels of these hormones and tumor aggressiveness. There have been controversial studies suggesting an inverse association between serum levels of free and total testosterone and a diagnosis of high-grade prostate cancer.^[2,10] It has been suggested that lowering androgen levels by using a 5 α -reductase inhibitor might favor the development of aggressive prostate cancer.^[2] We did not evaluate the relationship between the hormone levels and the histologic grade of the tumor, as this analysis was beyond the scope of this study. The influence of androgens on the grade of the tumor should be studied in a group that is uniform with regard to histological staging.^[10,11]

The effects of serum testosterone on benign prostatic hyperplasia (BPH) have also been studied. It has been found that higher serum testosterone levels are associated with a lower BPH risk (12). There have also been studies that have failed to show a correlation between serum testosterone levels and the development of BPH.^[8] The treatment of BPH includes 5 α -reductase inhibitors, which prevent the reduction of testosterone to dihydrotestosterone in the prostate gland.^[12] As previously mentioned, using 5 α -reductase inhibitors does not affect the risk of prostate cancer development but may favor the development of aggressive prostate cancers.^[2]

Isbarn et al.^[11] reviewed the literature on the effects of testosterone on prostate tissue, and they concluded that the

stimulatory effect of testosterone on benign and malignant prostate diseases does not increase beyond a saturation point. Therefore, increasing or decreasing serum testosterone levels beyond eugonadal levels does not alter the development of prostate diseases.^[11]

The testis is the organ that synthesizes testosterone. After the age of 30 years, the size of the testis does not change significantly. Testis volume is strongly correlated with sperm volume and quality and testosterone levels. If the Leydig cell function is preserved, the mean testosterone concentrations are normal regardless of the size of the testis.^[13] In both of our patient groups, testicular volumes and the levels of testosterone were within normal limits.

We know that although it is not specific, serum prostate-specific antigen (PSA) levels are the main predictor of prostate cancer. All men with a risk of prostate cancer are monitored via serum PSA. Another suggested predictor of prostate cancer is the ratio of serum testosterone to serum PSA (t/PSA).^[14] Nevertheless, the use of t/PSA as a predictor was not confirmed by a recent study of Morote et al.^[15] They concluded that t/PSA is not a useful predictor of prostate cancer risk and that there is no relationship between serum testosterone levels, prostate cancer development, and tumor aggressiveness.^[15] Therefore, a distinct role has still not been found for serum testosterone in the prediction of prostate cancer or in strengthening the specificity of PSA as a predictor.

The increase in the prevalence of benign and malignant prostate diseases in elderly men does not vary significantly in different countries. Nevertheless, the death rates from prostate cancer vary between various populations.^[16] Studies have been performed to investigate the relationship between genetic alterations (e.g., androgen receptor gene, steroid 5 α -reductase type II gene, etc.) and prostate cancer development, but these studies have also been inconclusive.^[10,17-19] Therefore, we believe that there is a complex relationship between androgenic activity and prostate cancer development that cannot be easily determined by measuring testosterone levels.

The limitation of our study is the limited number of patients with prostate cancer. For this reason, we could not group the patients according to Gleason scores. Further studies with larger numbers of patients would be advantageous to investigate estrogen levels and the expression of the androgen receptor and 5 α -reductase type II genes in patients with prostate cancer.

In conclusion, the effects of testosterone on the growth and differentiation of prostatic tissue are well known. Prolonged exposure to serum testosterone is related to the occurrence of benign and malignant prostate diseases. This effect has led many

Table 1. Comparison of prostate cancer (+) and (–) groups

	Prostate cancer + (n=32)	Prostate cancer – (n=70)	p value
Age (mean $\pm$ SD)	64.9 $\pm$ 6.4	60.9 $\pm$ 6.2	0.04
Total testosterone (mean $\pm$ SD)	484.6 $\pm$ 200.8	459.2 $\pm$ 132.5	0.449
Free testosterone (mean $\pm$ SD)	9.1 $\pm$ 4.3	11.1 $\pm$ 8.6	0.244
PSA (mean $\pm$ SD)	7.5 $\pm$ 0.7	7.1 $\pm$ 2.5	0.417
Testis volume (mean $\pm$ SD)	21.25 $\pm$ 4.65	20.68 $\pm$ 5.32	0.335

Table 2. Results of binary logistic regression analysis

	OR	95% CI	p value
Age	1.106	1.031-1.187	0.02
Total testosterone	1.002	0.999-1.005	0.213
Free testosterone	0.943	0.841-1.057	0.315
PSA	0.937	0.764-1.149	0.441
Testis volume	1.015	0.886-1.039	0.328

researchers to investigate the possible association between serum testosterone levels and prostate disease. Although management of both BPH and prostate cancer includes anti-androgen therapy, no consensus has been achieved on the role of testosterone in prostate cancer development. Our study failed to show a relationship between total and free serum testosterone levels, testis volume, and the risk of prostate cancer. Therefore, monitoring serum testosterone levels for prostate cancer prediction does not appear to confer an advantage over PSA screening. Because there is no scientific consensus on the effects of testosterone on prostate cancer, patients with low or high serum testosterone levels and patients undergoing testosterone therapy should be informed of the risks and their progress should be closely followed.

Conflict of Interest: No conflict of interest was declared by the authors.

References

1. Bostwick DG, Burke HB, Djakiew D, Euling S, Ho SM, Landolph J, et al. Human Prostate Cancer Risk Factors. *Cancer* 2004;101:2371-490.
2. Severi G, Morris HA, MacInnis RJ, et al. Circulating steroid hormones and the risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2006;15:86-91.
3. Chu LW, Reichardt JKV, Hsing AW. Androgens and the molecular epidemiology of prostate cancer. *Curr Opin Endocrinol Diabetes* 2008;15:261-70.
4. Hsing AW, Chu LW, Stanczyk FZ. Androgen and prostate cancer: is the hypothesis dead? *Cancer Epidemiol Biomarkers Prev* 2008;17:2525-30.
5. Morote J, Ramirez C, Gomez E, Planas J, Ranentos CX, Torres IM, et al. The relationship between total and free serum testosterone and the risk of prostate cancer and tumour aggressiveness. *BJU Int* 2009;104:486-9.
6. Parsons JK, Carter HB, Platz EA, Wright EJ, Landis P, Metter EJ. Serum testosterone and the risk of prostate cancer: potential implications for testosterone therapy. *Cancer Epidemiol Biomarkers Prev* 2005;14:2257-60.
7. Huggins C, Hodges CV. Studies on prostatic cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. 1941. *J Urol* 2002;168:9-12.
8. Stanworth RD, Jones TH. Testosterone for the aging male; current evidence and recommended practice. *Clin Interv Aging* 2008;3:25-44.
9. Endogenous Hormones and Prostate Cancer Collaborative Group, Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *J Natl Cancer Inst* 2008;100:170-83.
10. Platz EA, Leitzmann MF, Rifai N, Kantoff PW, Chen YC, Stampfer MJ, et al. Sex steroid hormones and the androgen receptor gene CAG repeat and subsequent risk of prostate cancer in the prostate-specific antigen era. *Epidemiol Biomarkers Prev* 2005;14:1262-9.
11. Isbarn H, Pinthus JH, Marks LS, Montorsi F, Morales A, Morgentaler A, Schulman C. Testosterone and prostate cancer: revisiting old paradigms. *Eur Urol* 2009;56:48-56.
12. Kristal AR, Schenk JM, Song Y, Arnold KB, Neuhauser ML, Goodman PJ, et al. Serum steroid and sex hormone-binding globulin concentrations and the risk of incident benign prostatic hyperplasia: results from the prostate cancer prevention trial. *Am J Epidemiol* 2008;168:1416-24.
13. Bahk JY, Jung JH, Jin LM, Min SK. Cut-off value of testes volume in young adults and correlation among testes volume, body mass index, hormonal level, and seminal profiles. *Urology* 2010;75:1318-23.
14. Karamanolakis D, Lambou T, Bogdanos J, Milathianakis C, Sourla A, Lembessis P, et al. Serum testosterone: A potentially adjunct screening test for the assessment of the risk of prostate cancer among men with modestly elevated PSA values ($>$ or $=$ 3.0 and $<$ 10.0 ng/ml). *Anticancer Res* 2006;26:3159-66.
15. Morote J, Planas J, Ramirez C, Gómez E, Raventós CX, Placer J, et al. Evaluation of the serum testosterone to prostate-specific antigen ratio as a predictor of prostate cancer risk. *BJU Int* 2009;105:481-4.
16. Jin B, Beilin J, Zajac J, Handelsman DJ. Androgen receptor gene polymorphism and prostate zonal volumes in Australian and Chinese men. *J Androl* 2000;21:91-8.
17. Pearce CL, Van Den Berg DJ, Makridakis N, et al. No association between the SRD5A2 gene A49T missense variant and prostate cancer risk: lessons learned. *Hum Mol Genet* 2008;17:2456-61.
18. Kraft P, Pharoah P, Chanock SJ, et al. Genetic variation in the HSD17B1 gene and risk of prostate cancer. *PLoS Genet*. 2005:e68. Epub 2005 Nov 25.
19. Nelson KA, Witte JS. Androgen receptor CAG repeats and prostate cancer. *Am J Epidemiol* 2002;155:883-90.