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Significance of Serum Testosterone for Prostate-Specific Antigen (PSA) Elevation and Prediction of Prostate Cancer in Patients with PSA Above 10 ng/ml

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Purpose: Testosterone is essential for the prostate gland's normal growth and development and is also a possible risk factor for prostate cancer. This study's aim was to determine the significance of serum testosterone for prostate-specific antigen (PSA) elevation and prostate cancer prediction in high-risk men.

Materials and Methods: The study included 120 patients with PSA >10 ng/ml who underwent a transrectal-prostate biopsy. Serum testosterone, prostate volume, and PSA density (PSAD) were checked in all patients. Patients were divided into two groups, patients with and those without prostate cancer; and testosterone-related factors, prostate volume, PSA, PSAD, age, prostate cancer prediction rate, and cancer aggressiveness were evaluated.

Results: Thirty-five patients (30.2%) were confirmed as having prostate cancer. The average serum testosterone level in patients without and in those with prostate cancer was 452.25±154.62 ng/dl and 458.10±158.84 ng/dl, respectively; average PSA was 17.58±9.02 ng/ml and 18.62±6.53 ng/ml, respectively; and average age was 69.02±7.52 years and 70.69±7.02 years, respectively ($p>0.05$). Hypogonadal and eugonadal patients showed no significant difference in cancer prevalence (30.3% vs. 32.0%, respectively). The testosterone level did not differ significantly in patients with and those without prostate cancer in either hypogonadal or eugonadal men ($p>0.05$). Serum testosterone showed no correlation with PSA, PSAD, or age in either group ($p>0.05$) and was unrelated to prostate cancer risk or aggressiveness ($p>0.05$).

Conclusions: In our study's results, serum testosterone at the time of diagnosis was unrelated to PSA elevation, prostate cancer risk, and aggressiveness.

Key Words: *Prostate-specific antigen; Prostatic neoplasms; Testosterone*

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INTRODUCTION

Testosterone is essential for the normal growth and development of the prostate gland and is also a possible risk factor for prostate cancer [1,2]. Huggins and Hodges's seminal work in the 1940s first demonstrated the hormone dependence of prostate cancer [3], consequently establishing testosterone as a key therapeutic target for managing prostate cancer. Androgen deprivation therapy to lower the serum testosterone level remains a standard treatment for advanced disease to the present day. Isbarn et al's recent studies, however, show a result opposite that of Huggins and Hodges, implying that testosterone neither increases the risk of prostate cancer nor causes cancer recurrence in men who have been treated successfully for prostate cancer [4]. A recent study by Morote et al showed that prostate cancer risk and tumor aggressiveness are unrelated to serum testosterone [5]. Other recent epidemiologic studies also have found no association between testosterone and prostate cancer [6-10].

Our main objective was to analyze the relationship between serum testosterone, prostate-specific antigen (PSA), and prostate cancer risk in high-risk patients.

MATERIALS AND METHODS

The study population consisted of 120 men with a PSA level of 10 ng/ml or higher. The data were collected from January 2008 to January 2010. To determine the relationship between testosterone, PSA, and prostate cancer risk in a high-risk group, we limited our study population to men with a PSA level of 10 ng/ml or higher. We excluded from this analysis men who were taking medications known to lower PSA, such as finasteride or dutasteride. All men were assessed by a transrectal ultrasound (TRUS)-guided biopsy of the prostate. Twelve cores were obtained and two extra biopsies were taken if hypoechoic or otherwise suspicious areas were noted on ultrasound.

Serum testosterone levels were measured by using a solid-phase competitive chemiluminescent enzyme immunoassay with the Advia Centaur® Immunoassay system (Bayer Health Care, Chicago, IL, USA). Blood samples were taken between 8 am and 10 am and were processed immediately.

We classified the men as hypogonadal if their serum testosterone level was <300 ng/dl, according to the criteria used by Rhoden et al [11].

For possible correlation between serum testosterone, PSA, and prostate cancer, we included age, PSA density (PSAD), prostate volume, and Gleason score for patients with prostate cancer. Statistical analysis was performed by using the Student's t-test, the Pearson correlation test, simple linear regression, and binary logistic regression. Odds ratios with 95% confidence intervals (CIs) for PSA, PSAD, serum testosterone, and age were determined to predict prostate cancer risk. All data are presented as the Mean±2 SD to define and characterize quantitative variables and as percentages to characterize qualitative variables; we considered a p-value <0.05 to be statistically significant.

RESULTS

Out of 120 patients, the samples of 85 (70.1%) patients were diagnosed as benign and those of 35 (29.2%) patients were diagnosed as being prostate cancer. There was no significant difference in the patient's average age, PSA, prostate volume, or testosterone between patients without and those with prostate cancer. Only PSAD differed significantly between the two groups (t-test, p=0.012) (Table 1). Hypogonadism was diagnosed in 24 men. Hypogonadal and eugonadal men did not differ significantly in cancer detection rate (30.2% vs. 32.0%, respectively). The testosterone level did not differ significantly between patients without and those with prostate cancer in either hypogonadal (248.16±50.41 ng/dl vs. 251.35±43.61 ng/dl, respectively) or eugonadal (501.52±137.06 ng/dl vs. 506.22±126.40 ng/dl, respectively) men (t-test, $p>0.05$). Testosterone was unrelated to age, PSA, PSAD, or prostate volume in both men without and those with prostate cancer, and prostate cancer aggressiveness also was unrelated to serum testosterone in prostate cancer patients ($p>0.05$) (Table 2). The binary logistic regression also confirmed that none of the variables used in this study was an independent predictor of prostate cancer risk for men with a PSA level >10 ng/ml

TABLE 1. Clinical and laboratory features in men with and those without prostate cancer

	Without prostate cancer (n=85, Mean±SD)	Prostate cancer (n=35, Mean±SD)	p-value
Age (yr)	69.02±7.52	70.69±7.02	0.265
Prostate volume (g)	41.48±17.10	36.77±16.73	0.171
PSA (ng/ml)	17.58±9.02	18.62±6.53	0.105
Serum testosterone (ng/dl)	452.25±154.62	458.10±158.84	0.852
<300	251.35±43.61	248.16±50.41	0.880
≥ 300	506.22±126.40	501.52±137.06	0.871
PSA density	0.26±0.18	0.37±0.26	0.012[a]

PSA: prostate-specific antigen, [a]: statistically significant

TABLE 2. Pearson correlation coefficients (p-value) for possible correlation with serum testosterone

	Benign biopsy	Prostate cancer
Age	−0.058 (0.597)	0.101 (0.565)
Prostate volume	−0.039 (0.720)	−0.211 (0.990)
PSA	−0.056 (0.611)	−0.241 (0.163)
PSA density	−0.083 (0.451)	−0.081 (0.6466)
Gleason score	-	0.239 (0.166)

PSA: prostate-specific antigen

TABLE 3. Binary logistic regression analysis of prostate cancer risk predictors

Variable	Odds ratio (95% CI)	p-value
Age	1.030 (0.97-1.093)	0.320
Prostate volume	1.002 (0.957-1.048)	0.937
Serum testosterone	0.999 (0.996-1.003)	0.646
PSA	0.999 (0.861-1.158)	0.986
PSA density	28.653 (0.99-8,252.572)	0.246

CI: confidence interval, PSA: prostate-specific antigen

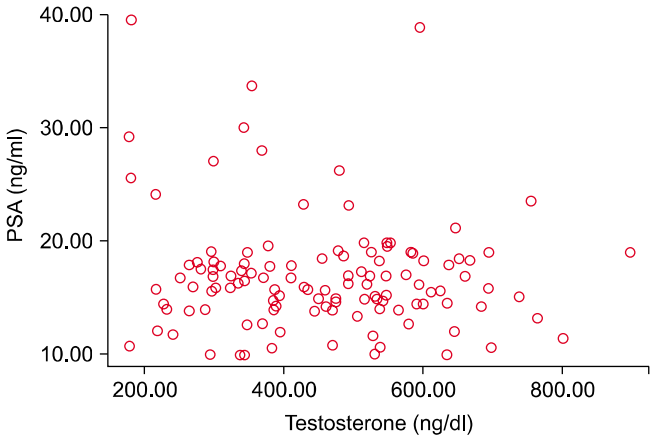

FIG. 1. Scatterplots showing the effect of testosterone on PSA. PSA: prostate-specific antigen.

TABLE 4. Prostate cancer prevalence according to testosterone levels

Testosterone range (ng/ml)	n	Cancer	Percentage
150-199	4	1	25.0
200-249	7	2	28.6
250-299	13	3	23.1
300-349	11	3	27.3
350-399	12	4	33.3
400-449	10	2	20.0
450-499	13	3	23.1
500-549	19	5	26.3
550-599	10	3	30.0
600-649	9	4	44.4
650 or higher	11	2	18.2

($p > 0.05$) (Table 3). Further evaluation with simple linear regression confirmed that testosterone and PSA did not show any correlation ($p > 0.05$) (Fig. 1). When we divided the patients into 11 groups according to their testosterone level, within a 150 ng/dl range, prostate cancer prevalence did not change as the testosterone level increased ($p > 0.05$) (Table 4).

DISCUSSION

In men, the Leydig cells in the testes produce approximately 90% of testosterone; the adrenal glands produce the rest. Testosterone plays a key role in the development of male reproductive tissues such as the testes and prostate gland [12]. Under testosterone influence, the prostate gland experiences two main growth periods. The first occurs early in puberty, when the prostate doubles in size. At around age 25, the gland begins to grow again. When the prostate is growing, testosterone is converted into dihydrotestosterone (DHT), which is the androgen receptor's major activator [13,14]. After DTH binds to androgen receptors, it translocates to the nucleus, where it mediates the transcriptional activation of target genes [15]. These androgen-stimulated changes in gene expression promote cellular growth, which often results in benign prostatic hyperplasia in elderly men.

Long-term cessation of the prostate's exposure to androgen appears to protect against the development of cancer, but no dose-response relationship between testosterone level and cancer risk has been established. The prostate cancer risk for men with a testosterone concentration in the normal range remains unclear [16]. Recent chemopreventive trials with 5-alpha-reductase inhibitors show the role of testosterone in prostate cancer development [17]. Finasteride reduced the risk of prostate cancer by 24.8% compared with a placebo in healthy men [18]. Recently, the REDUCE study showed that dutasteride also reduced the risk of prostate cancer by 23% compared with a placebo in healthy men [19].

Huggins and Hodges first showed the effect of testosterone on prostate cancer patients in 1941 [3]. They showed the hormonal responsiveness of prostate cancer by reporting that markedly reducing the testosterone level by castration and estrogen treatment caused metastatic prostate cancer to regress, and injecting testosterone caused prostate cancer to grow. In 1995 Wu et al found that the distribution of dihydrotestosterone-to-testosterone ratios parallels both the incidence of and mortality from prostate cancer [20].

The demonstration that androgen suppression effectively treats advanced prostate cancer, and the fact that elevated serum androgen levels might predispose people to prostate cancer, have attracted persistent interest. However, a recent study refuted any connection between elevated testosterone levels and increased prostate cancer risk [10,21]. Endogenous Hormones and Prostate Cancer Collaborative Group et al meta-analyzed the serum concentrations of sex hormones from subjects in 18 prospective studies that included 3,886 men with incident prostate cancer and 6,438 control subjects [10]. They concluded that endogenous hormones, including testosterone, were not associated with prostate cancer.

Morote et al recently conducted another study of 478 patients [5], all of whom were assessed by TRUS-guided prostate biopsy because of an abnormal digital rectal examination, PSA >4 ng/ml, or both. They found no difference in serum testosterone level between patients with and those without prostate cancer and concluded that the serum testosterone level was not associated with prostate cancer risk or aggressiveness.

An animal study by Morgentaler and Traish showed that beyond a certain serum testosterone concentration, androgens have a limited ability to stimulate prostate cancer growth [22]. Subsequent increases in serum testosterone levels beyond that concentration did not stimulate the prostate because the binding capacity of the intra-prostatic androgen receptors had been saturated.

Our results are similar to those of the above studies even though we limited our study population to patients with

PSA >10 ng/ml. We found that the serum testosterone level at the time of diagnosis was unrelated to PSA and prostate cancer risk and aggressiveness in both hypogonadal and eugonadal patients.

Ideas about the interaction between testosterone and prostate cancer have changed considerably over the past decade. Like our study, most recent epidemiologic studies have found no association between testosterone and prostate cancer [6-10]. A few studies published during the past decade contrast with our results, however, and show that low testosterone levels seem to be related to an increased risk of prostate cancer and tumor aggressiveness, such as a high Gleason score [23-28].

In our study, we compared age, PSA, prostate volume, and PSAD with testosterone. Only a known prostate cancer predictor, PSAD, showed a significant difference between patients with and those without prostate cancer, even in high-risk patients with a PSA level of 10 ng/ml or higher. Patients without prostate cancer had relatively lower PSA and larger prostates than did patients with prostate cancer. However, our binary logistic regression showed that PSAD was unsuitable as an independent predictor of prostate cancer risk in men with a PSA level of 10 ng/ml or higher. Furthermore, prostate cancer prevalence did not increase as testosterone levels increased.

Our study had several limitations. We measured the serum testosterone level in the patients only once, before their biopsy was done. Second, we checked only their total testosterone level and were unable to check their free testosterone level. Finally, our study population was smaller than those of other studies.

In summary, the present study found that the serum testosterone level at the time of diagnosis was unrelated to PSA and prostate cancer risk and aggressiveness. Because testosterone levels change with age and time, a prospective study with long-term testosterone monitoring is required to find a relationship between testosterone and prostate cancer.

CONCLUSIONS

Our results show that the serum testosterone level at the time of diagnosis was unrelated to PSA and prostate cancer risk and aggressiveness. Additional studies with long-term follow-up are needed to explain the possible mechanism and relationship between testosterone, prostate cancer, and PSA.

Conflicts of Interest

The authors have nothing to disclose.

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