



# Is There an Association Between Serum Prostate-Specific Antigen Values and Serum Testosterone Levels in Healthy Men?

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**Purpose:** To evaluate the relationship between levels of total testosterone and total prostate-specific antigen (PSA) in healthy men with PSA < 4 ng/mL.

**Materials and Methods:** The study comprised 179 men with a mean age of 59.19±12 years who visited Osmaniye State Hospital, Osmaniye, Turkey, between January 2006 and January 2007 for a routine checkup. The patients were divided into two subgroups: patients with PSA < 2.5 mg/ml (group I, n=160 patients) and patients with PSA of 2.5 to 4 ng/mL (group II, n=19 patients). The relationship between PSA and testosterone levels was investigated in both groups and in patients aged < 60 years. The mean testosterone level was calculated for patients aged < 50 years and was compared with the mean value of patients aged ≥ 50 years.

**Results:** In all patients, the mean values for serum PSA and total testosterone were 1.27±0.88 ng/mL and 404.04±158.86 ng/mL, respectively. No correlation was detected between serum PSA and testosterone levels in either subgroup (group I, r=0.072, p=0.363; group II, r=0.031, p=0.900) or in patients aged < 60 years (r=0.032, p=0.72). The mean values of testosterone in patients aged ≥ 50 years and in patients aged < 50 years were 417.01±163.35 and 344.16±120.21 ng/dL, respectively (p=0.02).

**Conclusions:** No impact of testosterone was found on the PSA level in healthy men with PSA < 4 ng/mL. Therefore, a high serum testosterone level may not mandate adjustment of PSA values. This serum sex hormone showed a significant increment after the age of 50 years. Further studies including a larger number of patients should be carried out to confirm these findings.

**Keywords:** Prostate; Prostate neoplasms; Prostate-specific antigen; Testosterone

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## INTRODUCTION

Prostate-specific antigen (PSA), a single-chain 33-kD glycoprotein serine protease, is produced almost exclusively by human prostatic epithelium. Although PSA lacks many of the qualities of an ideal tumor marker, it is the mostly widely used marker in the diagnosis and follow-up of prostate cancer [1]. Controversy exists regarding the use of PSA as screening test for prostate cancer owing to the lack of randomized trials showing a reduction in prostate cancer mortality. Moreover, the sensitivity and specificity of PSA limit its use as a screening tool because it is neither tissue

specific [2] nor cancer specific [3]. In addition, the serum PSA concentration is directly correlated with age and prostate volume and is known to differ across ethnic groups [4].

The liver has a significant role in the elimination of serum PSA but the kidneys and the lungs do not. Free PSA is eliminated by the kidney, but because of its molecular size, PSA bound to antichymotrypsin is cleared through the liver. Therefore, underlying liver disease may be a possible cause of a changing serum PSA level. However, no consensus has been reached regarding the influence of severe liver disease on the serum PSA level. Whereas some investigators have noted that serum PSA levels are not sig-

nificantly different among healthy men and men with liver cirrhosis or chronic hepatitis, others have demonstrated that the mean serum PSA level is significantly lower in men with liver cirrhosis than in healthy men [5,6].

Obesity is also associated with endocrine changes that have been implicated in the etiology of prostate cancer [7,8]. Some studies have investigated the relationship between obesity and PSA concentrations, and univariate logistic analysis indicated body mass index as a significant factor in relation to serum PSA [9]. Serum testosterone was suggested to be associated with a potentially atherogenic lipid profile, including high triglyceride and low high-density lipoprotein (HDL); furthermore, in healthy men, a decrease in endogenous testosterone was associated with an increase in HDL [10]. It is estimated that the lipid profile could affect serum PSA through the metabolism of serum testosterone. Also, testosterone was introduced as the expected mechanism by which body mass index and the lipid profile could affect the serum PSA level. However, the direct relation between the sex hormone and the PSA level is still ill defined, especially in healthy men. We conducted the present study in healthy men with a normal lipid profile and normal results on renal and liver function tests in order to solely evaluate the relation between PSA and testosterone.

## MATERIALS AND METHODS

A total of 179 patients with a mean age of  $59.19 \pm 12.00$  years who visited the outpatient clinic in Osmaniye State Hospital between January 2006 and January 2007 for a routine checkup were enrolled in this study. A digital rectal examination (DRE) was performed in patients aged 50 years or older. The patients' data are shown in Table 1. All patients underwent a detailed clinical examination. Blood samples were obtained for serum PSA determination, testosterone measurement, lipid profile, and renal function and liver function tests. The inclusion criteria were as follows: no lower urinary tract symptoms, normal urine analysis, normal urine culture, normal DRE, normal renal and liver function, no congestive heart failure, no ketoconazole or diuretics use, normal lipid profile, and PSA value less than 4 ng/mL.

**TABLE 1.** Comparison between the two groups

Variable	Group I (n=160)	Group II (n=19)	Total (n=179)
Age (y)	$58.44 \pm 12.12$	$66.29 \pm 8.15$	$59.19 \pm 12.00$
PSA (ng/mL)	$1.05 \pm 0.56$	$3.38 \pm 0.42$	$1.27 \pm 0.88$
Testosterone (ng/dL)	$401.46 \pm 1.57$	$432.35 \pm 1.71$ ( $p=0.59$ ) <sup>a</sup>	$404.40 \pm 1.58$

Values are presented as mean  $\pm$  standard deviation.

<sup>a</sup>.No significant difference was found in the testosterone level between groups.

PSA, prostate-specific antigen.

The patients were divided into two groups according to PSA values: patients with PSA values less than 2.5 ng/mL (group I), and patients with PSA values between 2.5 and 4 ng/mL (group II). The relation between the serum testosterone level and PSA values and age was evaluated in both subgroups, and testosterone levels were also calculated in each group. Fifty years of age was used as a cutoff value and the patients were divided into two groups and serum testosterone levels were compared between the groups. Similar evaluations were done for patients aged less than 60 years, i.e., mean age, mean testosterone level, and the relation between age, testosterone, and PSA levels.

All data are expressed as means  $\pm$  standard deviations. Independent-sample t-tests were used to compare blood test values between subgroups. Pearson correlation test was applied to estimate the correlation between testosterone levels and PSA values. The SPSS ver. 10.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. p-values of more than 0.05 were accepted as insignificant.

## RESULTS

In all patients, the mean serum PSA value and total testosterone level were  $1.27 \pm 0.88$  ng/mL and  $404 \pm 158.86$  ng/dL, respectively. Data on patients in the subgroups are summarized in Table 1. No correlation was detected between serum PSA values and serum testosterone levels in either the overall patients or the subgroups (group I:  $r=0.072$ ,  $p=0.363$ ; group II:  $r=0.031$ ,  $p=0.900$ ). In group I, age correlated weakly with testosterone and PSA levels; in group II, however, no significant correlation was detected among the same variables. No significant difference was detected between testosterone levels in either of the groups in Table 1 ( $p=0.59$ ).

For patients aged less than 60 years (119 patients), the mean PSA value, age, and testosterone level were  $1.10 \pm 0.78$  ng/mL,  $52.73 \pm 7.53$  years, and  $386.40 \pm 154.60$  ng/dL, respectively. When the relation between age and testosterone level was investigated in these patients, a significant positive relation was detected ( $r=0.22$ ,  $p=0.015$ ). However, no significant relation was detected between testosterone level and PSA values in patients aged less than 60 years ( $r=0.032$ ,  $p=0.72$ ). The mean testosterone levels in patients aged 50 years or older and in those aged less than 50 years were  $417.01 \pm 163.35$  and  $344.16 \pm 120.21$  ng/dL, respectively ( $p=0.02$ ).

## DISCUSSION

Most of the studies that have investigated the relationship between testosterone and PSA levels have been conducted in hypogonadal men who received replacement androgen therapy. Some of these studies reported a significant increase in the serum PSA level as the result of exogenous or endogenous androgen replacement. Thus, determining the PSA level before and after testosterone therapy is recommended. Any elevation in the PSA level after testos-

terone therapy should prompt performance of a urologic evaluation for possible prostate biopsy [11]. Others have reported that the PSA level remains stable after normalization of the testosterone level and that the incidence of prostate cancer among men with low-onset hypogonadism who are receiving testosterone replacement therapy is no greater than in the general population [11,12].

Our study differs from other studies in that we attempted to investigate the effect of the testosterone level on PSA values in healthy patients and to determine whether a high testosterone level may mandate adjustment of normal ranges of the PSA level. For example, some centers perform prostate biopsy in patients with  $\text{PSA} \geq 2.5$  ng/mL and other centers still consider  $\text{PSA} \geq 4$  ng/mL as an indication for prostate biopsy. We found no significant relation between PSA and the testosterone level in either patients with PSA values of 2.5 to 4 ng/mL or patients with  $\text{PSA} < 2.5$  ng/mL. This suggests that the serum testosterone level does not have an impact on the PSA level. Thus, we do not believe that there is a need to adjust PSA values according to the serum testosterone level. The serum testosterone level did not differ significantly between patients with PSA less than 2.5 ng/mL (group I) and patients with PSA between 2.5 and 4 ng/mL (group II). This also correlated with the fact that the testosterone level may not significantly affect the PSA level.

Testosterone shows an increment with age, and this is an important issue because high serum testosterone levels are reported to be associated with aggressive prostate cancer, for example, as in black Americans. When the patients in this study were evaluated as a whole, a weak correlation was shown between age and testosterone level. However, when the correlation between testosterone and age was tested for patients aged less than 60 years, a significant positive correlation was detected. Also, when the testosterone level was compared between patients aged  $< 50$  years and patients aged  $\geq 50$  years, a significant difference in the serum testosterone level was detected. Both of these findings confirm a high testosterone level with aging, which is the opposite of findings showing the testosterone level to decrease as patients age [13].

Aging results in an increase sex hormone binding globulin and a decrease in testosterone, dehydroepiandrosterone, estrogens, thyroid-stimulating hormone, growth hormone, insulin-like growth factor-1, and melatonin. In addition, the increase in sex hormone binding globulin (SHBG) with age further lowers the concentrations of free biologically active androgens [14]. Between the ages of 30 and 80 years, the mean free testosterone index (the ratio of serum total testosterone to SHBG) decreases by as much as 50% in men. Furthermore, approximately 1 in 10 men over the age of 50 years, a figure that increases to 1 in 5 men over the age of 60 years, has hypogonadal levels of serum testosterone [15]. Therefore, the findings of our study regarding the increment of the serum testosterone level with age are in contrast with our expectations. Thus, we do recommend further studies to evaluate the impact of these findings on

urologic diseases or prostate diseases (benign and malign). We should keep in mind, however, that although the testosterone level increased significantly with age, especially in patients aged less than 60 years, no significant effect of testosterone on serum PSA values was detected. This means that PSA as a biomarker cannot predict the unclear but well established effect of sex hormone on prostate cancer.

Despite decades of research on the relationship between testosterone and related diseases, such as cognitive function, urologic diseases, and prostate cancer, many questions remain. The relation between the testosterone level and prostate cancer is well established but ill defined. Some studies support that a high testosterone level is associated with more aggressive advanced prostate cancer, as in black Americans, but with no effect of the testosterone level on the incidence of prostate cancer [16,17]. Even in patients with a high serum level of testosterone, screening tests for prostate cancer and the use of a serum PSA threshold of 2.5 ng/mL for biopsy among African Americans are recommended [18] because these are considered risk groups. However, some studies reported the opposite and claimed that a low serum testosterone level is associated with worse clinical and pathological determinants of prostate cancer, such as a higher Gleason score [19,20], worse pathological stage [21], and worse 5-year biochemical relapse-free survival [22]. Whether the serum level of testosterone is low or high, the variation in the sex hormone level should be investigated so that the management of diseases that are reported to be in direct relation with this hormone can be adjusted accordingly. Therefore, patients with high serum testosterone can be considered a risk group for the development of prostate cancer with more aggressive oncologic features. Thus, screening tests with PSA and DRE can be valid for such patients. Hopefully, the result of such programs would be to increase the percentage of men diagnosed with organ-confined prostate cancer, especially among patients in high-risk groups. Therefore, we do recommend the determination of the sex hormone concentration for each nation in case variation in the testosterone level is present, which would thus result in variation in the characteristics of many urological and nonurological disorders.

Socioeconomic, environmental, dietary, and genetic factors are the most suspected and accepted explanation for the differences in testosterone levels, PSA values, incidence, and oncologic features of prostate cancer. However, little is known of the molecular genetic factors. Tumor suppressor genes or oncogenes play an important role in prostate cancer in black men. Therefore, increased research efforts are needed to understand this problem at the molecular level.

The low number of patients, absence of determinations of serum levels of free testosterone and prostatic tissue levels of testosterone and dehydrotestosterone can be considered to be limitations of our study.

## CONCLUSIONS

Although testosterone has documented importance in the control and progression of prostate cancer, no similar impact was detected on the serum PSA level. Therefore, we suggest that there is no need for adjustment of the serum PSA level according to the testosterone level in healthy men with PSA values less than 4 ng/mL. The impact of an increment in the serum level of testosterone on oncologic features of prostate cancer and other urologic diseases should be defined so that the management of prostate cancer in different regions can be adjusted accordingly. Further studies recruiting a larger number of patients from different regions should be carried out to verify our results.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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## EDITORIAL COMMENT

In treating hypogonadism, concern about the testosterone-induced prostate-specific antigen (PSA) increase has been perceived as one of the major limitation of testosterone replacement treatment (TRT). In this article [1] the authors made a hypothesis that healthy men with high serum testosterone level might have increased level of serum PSA, and we should count on it. However, their results proved no significant correlation between serum testosterone and serum PSA level.

There are major methodological issues to consider. The total number of men was too small and there were only nineteen men in group II, which could have limited statistical power of this study. Secondly, serum testosterone level in men has been shown to be decreased significantly with aging in both cross-sectional and longitudinal studies

[2]. But the results of this study concluded that serum testosterone level increased with age in younger group (<60 years old).

The basic concept that TRT induce minor PSA increase, which authors made their hypothesis from, is now confronted with contradictory data. In many systematic review papers, TRT does not cause significant elevation of serum PSA level [3]. Furthermore, Corona et al. [4] reported similar results that PSA was unrelated to testosterone concentration across most of the testosterone range. We are expecting more relevant results in this field, which could be helpful for our clinical practice, in near future.

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