

## Relationship between serum PSA and testosterone levels in two different geographic regions of Turkey

Türkiye'nin iki farklı coğrafi bölgesinde serum PSA ve testosteron düzeyleri arasındaki ilişki

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### Abstract

**Objective:** We aimed to evaluate the relationship between serum total testosterone and total prostate specific antigen (TPSA) levels in healthy men from two different regions of Turkey.

**Material and methods:** The study included two separate groups of healthy men from two geographically distinct regions in Turkey. Group 1 included 119 patients with a mean age of 52.73±7.53 years who visited Osmaniye State Hospital for routine check-up between January 2006 and January 2007. Group 2 consisted of 196 patients with a mean age of 50.32±7.84 years who were sent to outpatient clinics in İzmir Atatürk Teaching Hospital between July 2008 and July 2009. The relationships among testosterone and TPSA levels and patients' age were evaluated.

**Results:** The mean TPSA levels for Group 1 and Group 2 were 1.11±0.78 ng/mL and 1.75±1.06 ng/mL, respectively (p=0.5). The mean testosterone levels in Group 1 (386.4±154.6 ng/dL) and Group 2 (383.9±170.6 ng/dL) showed no significant difference (p=0.89). There was a positive correlation between the age of the patients and testosterone level (r=0.22, p=0.015) in Group 1; however, in Group 2, there was a significant negative correlation between age and serum testosterone levels (r=-0.16, p=0.022). Serum testosterone level showed no significant correlation with TPSA level in either group (Group 1: r=0.03, p=0.72; Group 2: r=-0.04, p=0.67).

**Conclusion:** Testosterone or TPSA levels did not change between geographical regions of Turkey. However, the effect of age on testosterone levels varies according to geographical regions. Further studies with more patients are needed to confirm these preliminary results and to investigate the impact of geographical regions on the oncologic features of prostate cancer and other urologic diseases.

**Key words:** Prostate cancer; prostate-specific antigen; testosterone.

### Özet

**Amaç:** Türkiye'nin iki farklı bölgesinde yaşayan sağlıklı erkeklerin serum total testosteron ve total prostat spesifik antijen (TPSA) düzeyleri arasındaki ilişkiyi araştırmayı amaçladık.

**Gereç ve yöntem:** Çalışma, Türkiye'nin iki farklı coğrafi bölgesinde yaşayan sağlıklı erkeklerden oluşturulmuş iki grup üzerinde yürütüldü. Grup 1, Ocak 2006-Ocak 2007 arasında rutin kontroller için Osmaniye Devlet Hastanesi'ne başvuran ve yaş ortalaması 52.73±7.53 olan 119 hastayı kapsarken, Grup 2 Temmuz 2008-Temmuz 2009 arasında İzmir Atatürk Eğitim ve Araştırma Hastanesi polikliniğine başvuran ve yaş ortalaması 50.32±7.84 olan 196 hastadan oluşmuştur. Testosteron ve TPSA düzeyleri ile hasta yaşı arasındaki ilişki değerlendirilmiştir.

**Bulgular:** Ortalama TPSA değerleri Grup 1 ve Grup 2 için, sırasıyla 1.11±0.78 ng/mL ve 1.75±1.06 ng/mL idi (p=0.5). İki grubun ortalama testosteron seviyeleri arasında anlamlı fark tespit edilmedi (Grup 1'de 386.4±154.6 ng/dL, Grup 2'de 383.9±170.6 ng/dL; p=0.89). Grup 1'deki hastalarda yaş ile testosteron düzeyi arasında pozitif bir ilişki (r=0.22; p=0.015) mevcut iken, Grup 2'de bu iki parametre arasında anlamlı bir negatif ilişki (r=-0.16; p=0.022) saptandı. Serum testosteron seviyesi ile TPSA değerleri arasında, hiçbir grupta anlamlı ilişki bulunmadı (Grup 1 için r=0.03, p=0.72; Grup 2 için r=-0.04, p=0.67).

**Sonuç:** Türkiye'de coğrafik bölgeler arasında bireylerin testosteron ve TPSA düzeyleri fark göstermemektedir. Yaşın testosteron üzerine etkisi coğrafik bölgeye göre değişmektedir. Çalışmamızdaki sonuçların teyit edilmesi ve coğrafik bölgenin prostat kanserinin onkolojik özellikleri ve diğer ürolojik hastalıklar üzerine etkisini araştırmak için daha fazla sayıda hasta içeren çalışmalara ihtiyaç vardır.

**Anahtar sözcükler:** Prostat kanseri; prostat spesifik antijen; testosteron.

The relationship between prostate cancer and androgen is well established. In 1941, Huggins and Hodges<sup>[1]</sup> reported the regression of metastatic prostate cancer in three men after a reduction in testosterone level, and the progression of metastatic disease and symptoms in a patient who was treated with exogenous testosterone. Since then, many reports have documented the importance of serum androgen in the progression and control of prostate cancer. However, there is a controversy regarding the role of androgen in the pathophysiology and clinical treatment of men at risk of prostate cancer. Two theories have been proposed to explain the relationship between prostate cancer and serum testosterone levels: suppression theories, which state that malignant prostate cells secrete androgen inhibitors,<sup>[2,3]</sup> and saturation theories, which state that levels of serum androgen above baseline levels are sufficient to stimulate prostate growth (benign or malignant). Although testosterone does not increase the incidence of prostate cancer, high testosterone levels in black men are associated with more aggressive prostate cancer. Notably, black men are considered to be at high risk of prostate cancer, and a screening test may be recommended. Moreover, there is a well-established, but ill-defined relationship between testosterone and prostate cancer. Therefore, it is logical to expect a relationship between testosterone and serum total prostate specific antigen (TPSA), because TPSA is secreted by epithelial cells, which respond to testosterone. In this prospective study, we assessed the relationship between serum testosterone and TPSA levels in two geographically distinct regions of Turkey by comparing the clinical variables of both groups.

### Materials and methods

The study included two separate groups of healthy men from two geographically distinct regions in Turkey. The first group consisted of 119 men with a mean age of 52.73±7.53 years who visited Osmaniye State Hospital for routine check-up between January 2006 and January 2007. The second group consisted of 196 men with a mean age of 50.32±7.84 years who visited out-patient clinics at İzmir Atatürk Teaching Hospital between July 2008 and July 2009. In general, the Osmaniye region population is characterized by a low socioeconomic level, a high-fat diet, and a climate that differs from that of the İzmir region. The

population inhabiting the İzmir region is characterized by high socioeconomic level, a low-fat diet and high fruit and vegetable consumption. The inclusion criteria for both groups were normal urine analysis and urine culture, normal renal and liver function tests, normal digital rectal examination for patients older than 50 years, and TPSA values <4 ng/mL. All patients were <60 years old; any patient who was diagnosed with chronic disease was excluded. Morning serum testosterone levels and TPSA values were determined for each patient in both groups. The relationship among serum testosterone level, TPSA values, and age of patients was evaluated in both groups. The mean values for TPSA and testosterone levels, and age were calculated for each group. Group means were compared.

### Statistical analysis

All data were expressed as mean±standard deviation (SD). Independent-sample t-test was used to compare blood test values. Pearson's correlation test was applied to estimate the correlation between testosterone levels and TPSA values. The SPSS for Windows 10.0 was used for statistical analysis, and p values less than 0.05 were considered statistically significant.

### Results

The mean values of TPSA and testosterone for both groups were similar. The mean TPSA in Group 1 and Group 2 were 1.11±0.78 and 1.75±1.06, respectively (p=0.5). The mean serum testosterone levels were 386.4±154.6 ng/dL in Group 1 and 383.9±170.6 ng/dL in Group 2 (p=0.89). The mean age of the patients in Group 1 (52.73±7.53 years) was higher than that of Group 2 (50.32±7.84 years) (p=0.008). Data on the association among testosterone levels, TPSA values, and ages are shown in Table 1. In Group 1, the testosterone level increased with patient age (r=0.22, p=0.015). However, in Group 2, there was a significant negative correlation between patient age and serum testosterone level (r=-0.16, p=0.022). The impact of testosterone on TPSA values was investigated in both groups. In Group 2, no association was detected between serum testosterone level and TPSA value (r=-0.04, p=0.67). In Group 1, there was also no statistically significant correlation between testosterone level and TPSA value (r=0.03, p=0.72).

## Discussion

Many reports support variation in testosterone level in individuals. It is likely that multiple factors are involved, including socioeconomic, environmental, dietary, and genetic factors. Black men have higher serum testosterone levels than white men. Black men present with more advanced disease at a younger age than white men with prostate cancer. The differences in androgen level described here were noted only in men  $\leq 40$  years of age. After age of 40 years, black and white men have comparable serum testosterone levels. In addition, although prostate growth is androgen dependent, no difference in serum testosterone levels was detected in men with and without prostate cancer.<sup>[4]</sup>

Total PSA level was reported to be increased in response to all types of testosterone replacement, regardless of whether the testosterone level was raised endogenously or exogenously.<sup>[5]</sup> However, other researchers claimed that TPSA levels remain stable after the normalization of testosterone and that the incidence of prostate cancer among men with low-onset hypogonadism (LOH) on testosterone replacement therapy (TRT) was no greater than that in the general population.<sup>[6]</sup> Marks et al.<sup>[7]</sup> investigated the effect of TRT on prostate tissue and suggested that TRT for 6 months in patients with LOH normalized serum androgen, but appeared to have little effect on prostate tissue androgen levels and cellular function. Rhoden et al.<sup>[8]</sup> evaluated prostatic changes in hypogonadal men with and without high-grade intraepithelial neoplasia (PIN), which is considered to be a prostatic precancerous lesion after one year of TRT. There was no significantly greater increase in TPSA or increased risk of cancer in men with PIN as compared to men without PIN.<sup>[8]</sup> Therefore, TRT is not contraindicated in men with a history of PIN.

Despite the large number of studies regarding the impact of testosterone on TPSA level and prostate

cancer, both of these issues remain to be defined. The difference in testosterone levels between populations inhabiting both regions was evaluated in an effort to isolate differences in oncologic features. There was no difference in the mean values of testosterone or TPSA levels between both regions. Therefore geographic region and dietary intake did not cause a significant difference in testosterone or TPSA levels. Therefore, the normal range of TPSA values may be applicable to all people in both regions; the suggested variation in the normal ranges of TPSA due to ethnic and geographic factors seems not to be applicable in Turkey.<sup>[9]</sup>

We found an inverse significant relationship between age and testosterone level in Group 2 and a positive correlation in Group 1. This is an important finding, because it is well known that testosterone levels decline with age;<sup>[10]</sup> there are many diseases or phenomena that may be affected by variations in testosterone level, such as cognitive function, attention, Alzheimer's disease, impotence, prostate cancer, and TPSA serum level.<sup>[11]</sup> The increase in testosterone level with age supports observations of high testosterone levels and more aggressive prostate cancer at a younger age among black men. Other studies have claimed that low testosterone levels might be related to worse clinical and pathological determinants of prostate cancer, including increased risk of prostate cancer,<sup>[12,13]</sup> worse 5-year biochemical relapse-free survival,<sup>[13]</sup> higher Gleason sums on biopsy,<sup>[14,15]</sup> increased percentage of positive-core rate at biopsy and worse pathological stage.<sup>[16,17]</sup> In light of the results of these preliminary studies, increased efforts toward patient awareness and TPSA screening are certainly warranted, especially in patients with high risk of developing prostate cancer characterized by more aggressive oncologic features. We believe that TPSA and DRE screening tests are necessary for men in Group 1.

Testosterone level showed no significant impact on TPSA values in both groups, although the testosterone level increased significantly in Group 1. A possible explanation for this finding could be that all of the studies that reported increased TPSA in response to any endogenous or exogenous hormone replacement<sup>[5]</sup> were performed in hypogonadal men. However, our study was performed in eugonadal healthy men. Even in the hypogonadal patients, TPSA was found to remain stable after normalization of

**Table 1. Pearson's correlation coefficient (r) for the association between serum testosterone level, age, and total prostate-specific antigen (TPSA) level**

	Group 1		Group 2	
	r	p value	r	p value
Age versus testosterone	0.22	0.015	-0.16	0.02
TPSA versus testosterone	0.032	0.72	-0.04	0.67

serum testosterone level.<sup>[6]</sup> Another acceptable explanation could be the findings of a study conducted by Marks et al.,<sup>[18]</sup> who reported that prostatic tissue levels of testosterone and dehydrotestosterone (DHT) were similar in black and white men. The author did not support the hypothesis of increased androgenic activity in black men.

The low number of study patients is one of the major limitations of our study. We recommend further studies with larger number of patients to define the oncologic map of prostate cancer in Turkey and to determine whether there is a need for different approaches or policies for screening and follow-up of prostate cancer according to the different regions in Turkey. Such programs could increase the percentage of men diagnosed with organ-confined prostate cancer, especially in patients in the high-risk group.

Socioeconomic, environmental, dietary, and genetic factors are the most common explanations for the differences in the testosterone level, TPSA value, and incidence and oncologic features of prostate cancer. Obesity is associated with endocrine changes, which have been implicated in the etiology of prostate cancer.<sup>[19,20]</sup> Serum testosterone is suggested to be associated with a potentially atherogenic lipid profile, including high triglyceride (TG) and low high-density lipoprotein (HDL) levels. In healthy men, the decrease in endogenous testosterone was associated with an increase in HDL.<sup>[21]</sup> Testosterone hormone was introduced as the expected mechanism by which body mass index and lipid profile could affect the serum TPSA level.

As a conclusion, there were no significant differences in testosterone and TPSA levels between the two different regions. Therefore, our study suggests that the normal ranges of TPSA and testosterone are applicable to both regions in Turkey. Serum testosterone levels and ages showed different relationships in geographical regions. The impact of this variation on oncologic features of prostate cancer and other urologic diseases should be defined; the management of prostate cancer in the different regions may be adjusted accordingly. Further studies with more patients from different regions should be carried out to verify our results.

#### Conflict of interest

No conflict of interest was declared by the authors.

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