TURKISH JOURNAL OF UROLOGY
Turkish Journal of Urology 2013; 39(1): 12-5 • doi:10.5152/tud.2012.003
UROONCOLOGY
Original Article

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

Serum testosteron düzeyi, testis hacmi, ve prostat kanser riski: aralarında basit bir ilişki var mı?

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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.

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Submitted:
05.06.2012

Accepted:
14.08.2012

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Available online at
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ÖZET

Amaç: Literatürde serum serbest ve total testosteron düzeyleri ve prostat kanseri arasındaki ilişki hakkında kesin olmayan sonuçlar bildirilmiştir. Biz kendi hasta grubumuzda total ve serbest serum testosteron düzeyleri, testis hacmi ve prostat kanseri arasındaki ilişkiyi araştırdık.

Gereç ve yöntemler: Alt üriner sistem semptomları ile üroloji polikliniğine başvuran 102 hastada serum total ve serbest testosteron düzeyleri ve serum PSA değerleri kayıt edildi. Anormal rektal muayene bulgusu ve/veya >4.0ng/mL serum PSA düzeyi nedeni ile bütün hastalara transrektal ultrasonografi (US) rehberliğinde prostat biyopsisi yapıldı. Bütün transrektal ve testis US incelemeleri ve biyopsileri aynı radyolog tarafından yapıldı. Testis uzunluğu, genişliği ve yüksekliği transvers ve longitudinal gri skala görüntülerde ölçüldü ve testis hacmi hesaplandı.

Bulgular: Prostat biyopsisi yapılan 102 hastanın 32'sinde prostat kanseri saptandı (%31.3) (prostat kanseri grubu). Geri kalan hastalar benign histopatolojik bulgulara sahipti (prostat kansersiz grup). Prostat kanseri ve benign histoloji grupları yaş, total ve serbest testosteron, PSA değerleri ve testis hacmi açısından karşılaştırıldı. Prostat kanseri olan hastaların ortalama yaşı daha büyük bulundu (p=0.04). Serum PSA, serbest testosteron ya da total testosteron ve testis hacmi açısından iki grup arasında anlamlı fark yoktu (p>0.05). İkili lojistic regresyon analizi ne serbest ne de total testosteronun prostat kanseri için belirteç olmadığını göstermiştir (sırasıyla p=0.315 ve 0.213). Sadece yaş prostat kanseri gelişimi açısından anlamlı bir faktör olarak bulunmuştur (p=0.02).

Sonuç: Çalışmamızda total, serbest serum testosteron düzeyleri, testis hacmi ve prostat kanseri riski arasında bir ilişki gösterilememiştir. Dolayısıyla prostat kanserini ön görmek için serum testosteron düzeylerine bakmak PSA taramasına katkı sağlıyor gibi görünmemektedir.

Anahtar sözcükler: Prostat kanseri; PSA; testis; testosteron.

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 converted to 5α-dihydrotestosterone by the enzyme 5α-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 5α-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] 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. Biopsies were taken using an automatic 18-G needle. 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±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.

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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 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 5α-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]

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

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

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 5α-reductase inhibitors, which prevent the reduction of testosterone to dihydrotestosterone in the prostate gland.[12] As previously mentioned, using 5α-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, the testes 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 per-

formed to investigate the relationship between genetic alterations (e.g., androgen receptor gene, steroid 5α-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 5α-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 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.

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