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Serum Dehydroepiandrosterone Sulfate Usage for Early Detection of Prostate Cancer in Men with Serum Prostate Specific Antigen Level between 2.5 and 4.0 ng/ml: A Pilot Study

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Aims: We prospectively evaluated the diagnostic value of serum prostate specific antigen (PSA)-based diagnostic parameters and serum dehydroepiandrosterone sulfate (DHEAS) level for early detection of prostate cancer in patients with serum PSA level between 2.5 and 4 ng/ml.

Materials and Methods: This study included 83 consecutive men with serum PSA levels between 2.5 and 4.0 ng/ml. All patients underwent transrectal ultrasound-guided prostate needle biopsy. Total PSA level, free/total PSA ratio, PSA density of the total volume (PSAD-TV), PSA density of the transition zone (PSAD-TZ), and serum DHEAS values were determined.

Results: Seventy-four patients (89.2%) had histopathologically confirmed benign prostatic hyperplasia and the remaining (10.8%) had prostate cancer. DHEAS was a significant predictor of prostate cancer compared to free/total PSA ratio, PSAD-TV and PSAD-TZ (P_{DHEAS} = 0.012, $P_{free/total\ PSA}$ = 0.326, $P_{PSAD-TV}$ = 0.884, $P_{PSAD-TZ}$ = 0.203). If the cut-off point of DHEAS was considered 1,700 ng/ml, sensitivity and specificity of DHEAS were 100% and 59.4%, respectively. This cut-off point might lead to avoiding 40.9% of unnecessary prostate biopsies.

Conclusions: Serum DHEAS seems to be a reasonable marker for early detection of prostate cancer and can avoid unnecessary prostate biopsy in patients whose serum PSA level is between 2.5 and 4 ng/ml.

Key Words: Prostate cancer, prostate specific antigen, dehydroepiandrosterone sulfate

Serum Prostat Spesifik Antijen Düzeyi 2.5-4 ng/mL Arasında Olan Erkeklerde Prostat Kanserinin Erken Tanısı İçin Serum Dihidroepiandrosteron Sülfat Kullanımı: Pilot Çalışma

Amaç: Prostat spesifik antijen (PSA) düzeyi 2.5-4 ng/mL arasında olan hastalarda prostat kanserinin erken tanısı için PSA bağımlı tanısal değişkenler ve dihidroepiandrosteron sülfat'ın (DHEAS) tanısal değerini inceledik.

Yöntem ve Gereç: Bu çalışmaya PSA düzeyi 2.5-4 ng/mL arasında olan 83 erkek dahil edildi. Tüm hastalara transrektal ultrasonografi eşliğinde prostat iğne biyopsisi yapıldı. Total PSA düzeyi, free/total PSA oranı, total volum PSA dansitesi (PSAD-TV), transizyonel zon PSA dansitesi (PSAD-TZ) ve serum DHEAS düzeyleri belirlendi.

Bulgular: Yetmişdört hastada (% 89.2) histopatolojik olarak benign prostat hiperplazisi ve geri kalanlarda (%10.8) prostat kanseri saptandı. DHEAS prostat kanseri için free/total PSA oranı, PSAD-TV ve PSAD-TZ ile karşılaştırıldığında anlamlı bir belirleyiciydi (P_{DHEAS} = 0.012, $P_{free/total\ PSA}$ = 0.326, $P_{PSAD-TV}$ = 0.884, $P_{PSAD-TZ}$ = 0.203). DHEAS için kestirim noktası 1,700 ng/ml düşünülseydi, duyarlılık ve seçicilik sırasıyla % 100 ve % 59.4 olurdu. Bu kesitirim değeri % 40.9 gereksiz prostat biyopsisinden kaçınmayı sağlayabilirdi.

Sonuç: Serum DHEAS, serum PSA düzeyi 2.5-4 ng/mL arasında olan hastalarda prostat kanserinin erken tanısı ve gereksiz prostat biyopsisinden kaçınabilmek için makul bir belirleyici gibi görünmektedir.

Anahtar Sözcükler: Prostat kanseri, prostat specifik antijen, dihidroepiandrosteron sülfat

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Introduction

Prostate cancer is the most common estimated cancer among men and is alone responsible for approximately 33% of incidental cases in men (1). Regular serum prostate specific antigen (PSA) evaluation and digital rectal examination (DRE) are recommended for detecting prostate cancer (2). When a serum total PSA cut-off level

for biopsy of either 2.5 or 4.0 ng/ml is used, positive predictive values are similar (3,4). Thus, to avoid unnecessary biopsies in these patients and to detect prostate cancer more precisely, novel tumor markers are needed.

The major androgen in the male circulation is testosterone, 95% of which is from the testicles; adrenalin glands produce the remaining 5%. Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS), androgens of adrenalin origin, reach their plasma peak levels at about 25 years of age and decrease by 95% of the peak level at the age of 85 (5). Various prospective and retrospective studies have shown that decreased serum levels of DHEA and its sulfated compounds increase the risk of cancers such as breast, ovarian, and bladder cancers (6-9).

The aim of the present study was to investigate the efficacy of using serum DHEAS level in patients with serum total PSA level ranging from 2.5 to 4.0 ng/ml in the diagnosis of prostate cancer.

Materials and Methods

Between May 2001 and June 2007, 83 consecutive patients with serum total PSA levels between 2.5 and 4.0 ng/ml and/or abnormal DRE findings were included in this study. The patients underwent prostate biopsy under the guide of transrectal prostate ultrasonography (TRUS). Exclusion criteria were: previous prostate biopsy, previous treatment for chronic prostatitis, bladder tumor, active urinary tract infection, history of finasteride usage within the last year, ejaculation in the last 24 hours, urethral catheter associated with urinary retention, use of anticoagulant drugs, chronic liver and/or kidney disease, and any endourological procedure in the last 45 days.

Before the biopsy procedure, blood samples were taken by venipuncture from the antecubital region. Serum total and free PSA levels were measured by chemiluminescence method (Roche Diagnostics® GmbH, Germany; reference value: 0-4.0 ng/ml). Serum DHEAS was evaluated with Elecysis 2010. Serum DHEAS levels between 240 and 4920 ng/ml for those aged 10 to 19 years, 900 and 4920 ng/ml for those 20 to 44 years, and 400 and 3310 ng/ml for those 45 to 75 years are considered normal using this method.

Following blood collection, the patients underwent DRE. The presence of asymmetry, nodule in the prostate and/or irregularity of prostate contour were considered as abnormal findings. TRUS and biopsy procedures were performed using a 7.5 mHz biplane transrectal probe on Hitachi EUB 420 (Hitachi, Japan) ultrasonography device. The patients were in left decubitus position during the procedure. Hypoechoic area on TRUS and/or contour irregularities in the prostate were considered abnormal findings. To calculate total prostatic volume (TV) and transitional zone (TZ) volume of the prostate, ellipsoid formula was used at the time of TRUS.

During the biopsy procedure, an 18-gauge automatic prostate biopsy needle was used. In addition to sextant biopsy, lateral and far lateral biopsies were taken, two from each gland.

The patients were divided into two groups according to their histopathological results as those with prostate cancer (Group 1, n=9) and those without prostate cancer (Group 2, n=74). The groups were compared regarding age, serum total and free PSA levels, free/total PSA ratio, serum DHEAS levels, TV, TZ, and PSA density of the whole prostate (PSAD-TV) and of the transition zone (PSAD-TZ).

Statistical Analysis

Statistical Package for Social Sciences for Windows (SPSS, Chicago, USA) version 13.0 software was used for statistical evaluation of the results. The comparisons were performed by using Mann-Whitney test. Receiver Operating Characteristics (ROC) curve was drawn to evaluate the performance of serum DHEAS in diagnosing prostate cancer and to determine the best cut-off value for serum DHEAS. The sensitivity, specificity and positive predictive values were calculated. A P value less than 0.05 was considered statistically significant.

Results

The mean age of the patients was 62.6±7.01 (range: 45 to 74) years. The mean age in Groups 1 and 2 were 65.3±7.8 (range: 50 to 74) and 62.3±6.9 (range: 45 to 73) years, respectively (P: 0.170). There was no significant difference in terms of serum total PSA level, free/total PSA ratio, TV, TZ, PSAD-TV, and PSAD-TZ values between the groups. The demographic characteristics of the patients are shown in Table.

Table. Patients' demographic data.

PARAMETERS	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	P value
Age (year)	65.33 ± 7.84 (50-74)	62.27 ± 6.89 (45-73)	0.17
PSA (ng/ml)	3.34 ± 0.54 (2.54-4.0)	3.19 ± 0.44 (2.5-3.96)	0.368
Free/total PSA ratio	0.26 ± 0.17 (0.07-0.68)	0.19 ± 0.11 (0.04-0.77)	0.326
DHEAS (ng/ml)	953 ± 500 (148-1683)	1967 ± 1096 (96-3906)	0.012*
PSAD-TV	0.07 ± 0.02 (0.05-0.11)	0.08 ± 0.3 (0.02-0.17)	0.884
PSAD-TZ	0.20 ± 0.08 (0.11-0.32)	0.18 ± 0.11 (0.04-0.47)	0.203
TV	46.68 ± 6.56 (35-55)	50.24 ± 25.94 (21-205)	0.72
TZ	18.22 ± 5.64 (9-27)	24.13 ± 15.51 (7-100)	0.337

Data presented as mean ± standard deviation with minimum-maximum values in parentheses.
SD: standard deviation PSA: prostate specific antigen DHEAS: dehydroepiandrosterone sulfate PSA-TV: prostate specific antigen density of the whole prostate PSA-TZ: prostate specific antigen density of the transitional zone TV: total volume of the prostate TZ: transitional zone volume of the prostate.

At the end of the histopathological evaluation, prostate cancer was detected in 9 (10.8%) of the patients. In the evaluation of DRE findings, 25 (30.1%) of 83 patients had abnormal and 58 (69.9%) had normal findings. In Group 1, 4 (44.4%) patients had normal and the remaining (55.6%) had abnormal DRE findings. In Group 2, 54 (73%) patients had normal and 20 (27%) had abnormal DRE findings. The sensitivity, specificity and positive predictive value of DRE were 55.6%, 73%, and 20%, respectively.

In Group 1, TRUS findings were normal in 3 (33.3%) patients and abnormal in 6 (66.7%) patients. In Group 2, 66 (89.2%) and 8 (10.8%) patients had normal and abnormal TRUS findings, respectively. Prostate cancer was diagnosed in 6 (42.9%) of the 14 patients with abnormal TRUS findings. The sensitivity, specificity, and positive predictive value of TRUS were 67.7%, 89.2%, and 42.9%, respectively.

The mean DHEAS level in patients with prostate cancer was 953±500 (range: 148 to 1,683), and the mean DHEAS level in patients without prostate cancer was 1,967±1,096 (range: 96 to 3,906) ng/ml (P: 0.012). According to the ROC analysis, the best cut-off value of serum DHEAS was found as 1,700 ng/ml. Area under the ROC curves for serum DHEAS level was 0.758 (95% confidence interval [CI]: 0.649-0.868, P: 0.012) (Figure). When the cut-off value of DHEAS was considered as 1,700 ng/ml, the sensitivity and specificity of DHEAS were 100% and 59.4%, respectively.

Discussion

Serum total PSA level, DRE, and TRUS are the best-known diagnostic tools for prostate cancer. The role of TRUS in prostate cancer diagnosis has been debated. The most significant indication of TRUS is its guidance in needle biopsy procedures on systematic or suspected

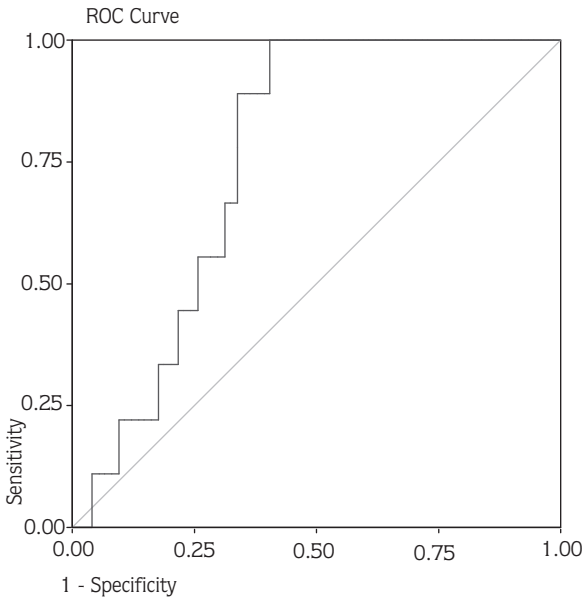

Figure 1. The ROC curve for serum DHEAS level. DHEAS: Dehydroepiandrosterone sulfate

areas. Nevertheless, both DRE and TRUS may lead to false-negative or false-positive results. DRE has been reported to have a positive predictive value of 21-53% (10-11). Ellis et al. (12) reported the diagnostic reliability of hypoechoic lesion on peripheral zone (PZ) as 43%, sensitivity as 85.5%, specificity as 28.4%, and positive predictive value as 29%. Our results in the present study were in agreement with their study.

Serum total PSA is one of the most commonly used tumor markers. It offers a contribution to the early diagnosis of prostate cancer (10). However, the cut-off value of serum total PSA level for prostate biopsy has been a matter of extensive debate. When total PSA cut-off level is considered high, some clinically important cancers may be overlooked. In contrast, when it is considered low, unnecessary biopsies would increase with associated morbidity and cost. The upper limit of serum total PSA level is usually considered as 4.0 ng/ml. However, approximately 20% of prostate cancer patients have serum total PSA levels below 4 ng/ml (13). In some studies, prostate cancer detection rate was between 2-28% in patients who had less than 4.0 ng/ml serum PSA level (14-16). Thus, patient selection, core number, core localization, and the suitable re-biopsy time are still controversial issues in prostate biopsy (17). Colberg et al. (18) reported that prostate cancer detection rate was 7.2% in 121 volunteers with suspicious DRE and/or TRUS and serum total PSA level between 2.9-4.0 ng/ml. Catalona and co-workers (13) diagnosed prostate cancer in 22% of 332 patients with serum total PSA level between 2.6-4.0 ng/ml, but they did not detect suspicious DRE and/or TRUS findings. In a study by Babaian et al. (14), 151 volunteers had serum total PSA value between 2.5-4.0 ng/ml, and prostate cancer was found in 24.5% of them. Another study evaluated 883 patients with serum total PSA level between 2.0-3.9 ng/ml, and prostate cancer rate was 14.3% (19). Clinically important cancers, 20% of which were beyond prostate, were reported in 89% of the patients with serum total PSA level less than 4.0 ng/ml (14). In the patients with serum total PSA value of 2.5-4.0 ng/ml, free/total PSA ratio, TV, TZ, PSAD-TV, and PSAD-TZ evaluations have not been described as fully efficient in differentiation of prostate cancer from benign disorders of the prostate (20,21). Thus, there is no parameter with verified efficacy in the diagnosis of prostate cancer. Since these parameters yielded similar results in both groups, new parameters are needed.

There are some studies in the international literature about serum DHEAS and the prostate cancer relationship. In a study by Stahl and colleagues (22), serum DHEA level was significantly lower in prostate cancer patients than in those without prostate cancer. In a study by Comstock et al. (23), low serum DHEAS levels were detected in 11% and 12% of the patients in the prostate cancer group and control group, respectively, with no significant difference between the groups. They thus concluded that serum DHEA and DHEAS levels were not a risk factor for prostate cancer. In contrast, two current studies found that serum DHEA levels were significantly lower in black patients than whites (24,25). They claimed that black patients are more prone to develop prostate cancer due to low serum DHEA level. On the other hand, Eaton et al. (26) evaluated the changes in the sex hormone values of patients with prostate cancer and normal men in a series of eight prospective epidemiological studies, and they found no difference between the serum DHEAS levels in the two groups. In another study, no significant difference was found in terms of serum DHEAS levels between patients with prostate cancer and benign disease (27). In our study, serum DHEAS levels in the prostate cancer group were significantly lower than those of the benign group. In this pilot study, we also aimed to

determine a clinical cut-off value for serum DHEAS level. To this end, a ROC curve was prepared and the best cut-off value of DHEAS was found to be 1,700 ng/ml. Prostate cancer diagnosis was not missed in our patients using this cut-off value.

Another important result of our study is that 10.8% of the patients had histopathologically proven prostate cancer. Our prostate cancer rate was lower than in the international literature. Two studies from our country revealed that the age-adjusted PSA reference ranges are greater than those universally accepted, and the prostate cancer detection rate is surprisingly low (17.5% versus 7.5%) in the PSA ranges between 4.0 and 10.0 ng/ml (28,29). In addition to ethnic characteristics, prostatic calculi and prostate inflammation may be contributing factors to PSA elevation (28,30).

In the present study, prostate cancer was detected in 10.8% of the patients. Serum DHEAS level may be useful in the differentiation of malignant and benign diseases of the prostate. Our results showed that low DHEAS level might be considered as a parameter before planning for a biopsy procedure in patients with serum total PSA level between 2.5 and 4.0 ng/ml. To our knowledge, our study is the first regarding early diagnosis of prostate cancer based on serum DHEAS levels in patients with serum total PSA level between 2.5-4.0 ng/ml. We believe further studies involving larger series are necessary before more definite conclusions can be drawn.

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