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ORIGINAL ARTICLE

Effects of antibacterial therapy on PSA change in the presence and absence of prostatic inflammation in patients with PSA levels between 4 and 10 ng/ml

O Kaygısız, Ö Uğurlu, M Koşan, G İnal, B Öztürk and M Çetinkaya
Department of Urology, Ankara Numune Education and Research Hospital, Ankara, Turkey

We investigated the effect of prostatic inflammation on prostate-specific antigen (PSA) and per cent-free PSA levels changing after antibacterial therapy. We evaluated 48 patients whose PSA levels were between 4 and 10 ng/ml, without any suspicious findings on digital rectal examination, with no infection findings in urine analysis. Prostatic inflammation was assessed with prostatic massage. All the patients were given antibiotic therapy for 3 weeks. Patients were re-evaluated 3 weeks after antibacterial therapy with PSA (free/total) and urinalysis. Ten core biopsies were taken with transrectal ultrasound. No differences were found in terms of age, pre- and post-treatment PSA, and PSA varying between patients with and without inflammation in the prostatic massage. In 18 patients, PSA decreased below 4 ng/ml. Prostate cancer was found in 10.8% of the patients with PSA between 4 and 10 ng/ml and none of the patients with PSA values below 4 ng/ml. We suggest an antibiotic therapy for 3 weeks without regarding inflammation findings when PSA is in the gray zone, for biopsy decision.
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Introduction

Prostate cancer is a frequent cancer that might have the chance of cure with early diagnosis. However, when digital rectal examination (DRE) is normal, the prostate-specific antigen (PSA) is 4.1–10 ng/ml; where the localized disease is seen frequently, prostate cancer can be found only with a ratio of 20–30%.[1,2] This causes additional morbidity in many patients. For this reason, many approaches have been developed in the literature, such as free PSA (fPSA) ratio, PSA density (PSAD) and PSA velocity (PSAV); however, none of these can completely eliminate the need for biopsy.[3]

Acute prostatitis is one of the well-established causes of PSA elevation.[4] Moreover, in many of the biopsy-based studies, it has been reported that prostate inflammation is related to elevated PSA.[5–7] In addition, it has been shown that biopsy can be avoided following antibiotics therapy in many patients in whom inflammation was found in the prostatic secretion in the PSA gray zone.[8–10] However, treatment of chronic prostatitis diagnosed with the determination of inflammation in the prostatic secretion results in taking direct biopsies in almost half of the patients.[9,10] In this study, we examined the effect of prostatic inflammation on PSA changing, by testing PSA levels after antibacterial therapy in patients with and without inflammation in prostatic secretion.

Materials and methods

Fifty-three patients with PSAs in the gray zone (4–10 ng/ml) with no suspicious findings in DRE and no urinary tract infection findings applying to the Urology Outpatient clinic between September 2003 and October 2004 were included in the study. One of the patients out of 56 was excluded from the study because of abnormality in the repeat DRE, one patient because of lung cancer history, one with chronic lymphositic lymphoma, one with the reason of four blind biopsies in another center and four because of not coming to control visits. The remaining 48 patients were included in the study.

The same experienced urologist performed all DREs. Absence of hard nodules, asymmetry and hardness was considered as a normal DRE. Prostatic secretion was obtained during DRE with prostatic massage, for patients in whom a sufficient amount of secretion had not been obtained; first urine following the massage (VB3) was taken. Secretion obtained with prostatic massage was examined in 7–8 areas with great magnification ($\times 400$) under the microscope; the presence of leukocytes more than an average of 10 in each area was

Correspondence: Dr O Kaygısız, Department of Urology, Ankara Numune Education and Research Hospital, Bahçeli Yeşilvadi sitesi, No: 7, Çayyolu/Yenimahalle, Ankara 06810, Turkey.
E-mail: onurkygsz@yahoo.com
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considered as positive expressed prostate secretion (EPS). Prostatic secretion and VB3 samples were sent for culture. PSA measurement was performed using Abbott AXSYM total PSA (3C19) and free PSA (3C20) kit.

All the patients included in the study were given antibiotic therapy with ofllоxacin 400 mg once a day for 3 weeks. For the patients in whom fluoroquinolone-resistant bacteria were found in the culture, bacteria-sensitive antibiotics were given for 3 weeks.

Patients were re-evaluated 3 weeks after antibacterial therapy with PSA (free/total) and urinalysis. Pre- and post-treatment PSA values were used to calculate the PSA change. PSA change was calculated according to the formula (PSA after therapy−PSA initial/initial PSA) × 100.

The same experienced urologist evaluated the patient after the treatment with transrectal ultrasound (TRUS), and 10 core (sextant + two lateral + two anterior horn) biopsies were taken simultaneously. A Hitachi EUB-400 ultrasonography device and 6.5 MHz transrectal probe were used in TRUS. Ellipsoid formula (0.52 × transverse diameter × anteroposterior diameter × cephalocaudal diameter) was used in calculating the prostate volume.[23] Spring-loaded 18 G biopsy needles were used in biopsies. The biopsy procedure was performed with the patient lying in left lateral decubitus position. Antibiotics prophylaxis was performed with ciprofloxacin 500 mg twice a day for 5 days starting from the day before the biopsy.

All statistical evaluations were carried out by SSPS 10.0 package program. All the data are given as mean ± s.d. Pre- and post-treatment PSA values and fPSA ratios were compared using paired *t*-test. Parameters for EPS (+) and (−) patient groups were compared using independent *t*-test. A total sample size of 48 achieve 80% power to detect a difference of 20.0 in PSAV between two groups with a significance level of 0.05 using a two-sided two-sample *t*-test. At the end of the analyses, a value of $P<0.05$ was considered statistically significant.

Results

The average age of the 48 patients was 65.02 ± 8.24 years. EPS was positive in 25 patients. Pathogen microorganisms were determined in five patients out of 25 patients. Methicillin-resistant *Staphilococus aerus* in one patient, coagulase-negative *Staphilococus* in two patients, *Escherichia coli* in one and *Corynebacterium propinqum* in one patient were determined. Cefuroxime axetil treatment was given to one patient for 3 weeks, in whom the pathogen microorganism was not sensitive to quinolone group antibiotics.

Whereas the average pre-treatment PSA was 6.53 ± 1.64 ng/ml for the entire patient group, the PSA level decreased to 4.76 ± 1.9 ng/ml in the post-treatment period. Reduction in PSA after the treatment was statistically significant (Figure 1a). The average PSA change was −23.36 ± 31.34% (Figure 1b), whereas five culture-positive patients' average PSA change was −17.99 ± 36.52%. fPSA significantly reduced after the treatment, and the percentage of free PSA increased significantly for the entire patient group (Table 1).

No differences were found in terms of age, pre- and post-treatment PSA and PSA varying between patients with and without inflammation findings in the prostatic massage (Table 2). In addition, parameters of the patients with and without growth in culture were also alike (Table 2).

Ten patients out of 48 coming for a control visit after antibiotic therapy refused biopsy. Two of them had over 4 ng/ml post-treatment PSA values.

The mean age of patients from whom biopsies were taken was 64.9 ± 8.27 years. Whereas the pre-treatment mean PSA value in patients from whom biopsies were taken was 6.65 ± 1.64 ng/ml, the post-treatment mean PSA decreased to 5.16 ± 1.88 ng/ml. Post-treatment PSA had decreased significantly ($P=0.014$). PSA change was 18.4 ± 31.08%. Mean volume was 59.3 ± 21.7 ml. PSA values decreased in 31 patients out of 38, and in 10 patients among these PSA decreased below 4 ng/ml.

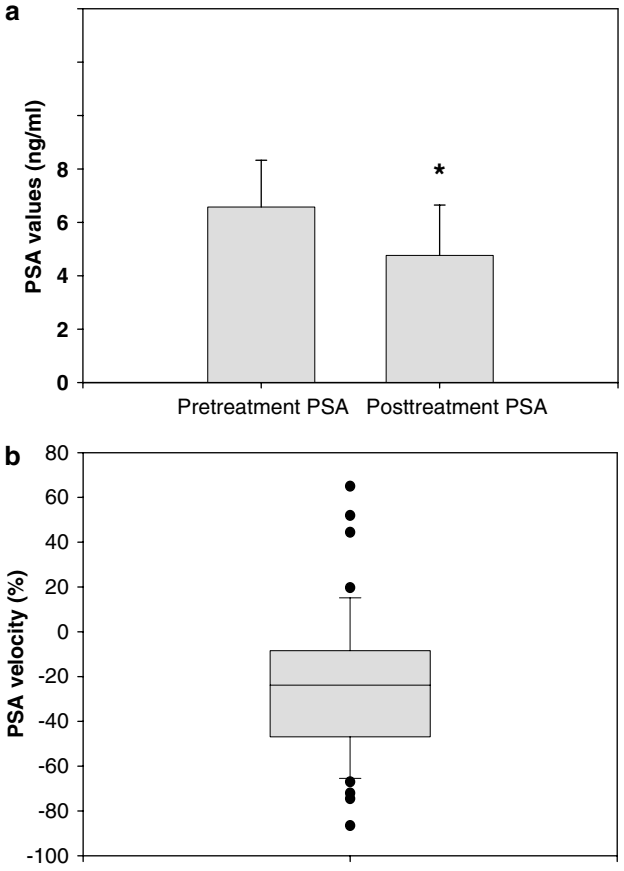


Figure 1 (**a**) Pre- and post-treatment PSA values. (**b**) PSA change after the treatment. (*$P<0.01$; pre- and post-treatment PSA values significantly different).

Table 1 Comparison of pre- and post-treatment parameters

	Initial	*Post-treatment*	P-*value*
PSA	6.53 ± 1.64	4.76 ± 1.89*	0.023
fPSA	1.31 ± 0.65	1.01 ± 0.6*	0.001
Per cent fPSA	19.54 ± 7.4	22.2 ± 10.4*	0.004

Abbreviations: fPSA, free prostate-specific antigen; PSA, prostate-specific antigen.
*Significant changes in post-treatment parameters, $P<0.05$ significant

Table 2 Comparison of parameters in patients with and without (a) EPS inflammation findings (independent *t*-test, $P<0.05$ significant) and (b) positive culture in EPS (+) patients

	EPS (−) (n = *23)*	*EPS (+)* (n = *25)*	P-*value*
Age	65.14 ± 8.5	64.65 ± 8.12	0.85
Pre-treatment PSA	6.38 ± 1.38	6.77 ± 2.07	0.55
Post-treatment PSA	4.41 ± 1.48	5.12 ± 2.13	0.21
PSA change (%)	−28.9 ± 23.94	−17.5 ± 37.23	0.22
	Culture (−) (n = *20)*	*Culture (+)* (n = *5)*	
Age	65 ± 8.14	66.8 ± 9.04	
Pre-treatment PSA	6.99 ± 1.96	5.35 ± 0.94	
Post-treatment PSA	5.43 ± 2.2	4.22 ± 1.45	
PSA change (%)	−15.9 ± 36.13	−17.99 ± 36.5	

Abbreviation: PSA, prostate-specific antigen.

Table 3 Inflammation ratio in patients with EPS (+) and (−)

	EPS	
	Negative n *(% within EPS)*	*Positive* n *(% within EPS)*
Inflammation		
Negative	15 (83.3%)	16 (80%)
Positive	3 (16.7%)	4 (20%)

Whereas inflammation in biopsy following the antibiotic therapy was observed in three patients out of 18 that EPS was negative (16.7%), it was observed in four out of 20 in patients with positive EPS (20%) (Table 3).

Suspicious foci (a focus of atypical glands) were found in the biopsies of four patients. One patient refused re-biopsies. At re-biopsy, prostate cancer was determined in one patient. Prostate cancer was determined in four patients; their PSA levels remained over 4 ng/ml. Two of them had elevated PSA (29%) after antibacterial therapy and two of them had decreased PSA (6.6%). When the patients with a focus of atypical glands was found but on whom re-biopsies were not performed were excluded, cancer was found in 10.8% of the patients among those in whom PSA was over 4 ng/ml.

Comment

Prostate cancer is determined in only 34% of the biopsies performed because of PSA elevation.[11] As the ratio of finding prostate cancer in patients with normal DRE and PSA values between 4 and 10 ng/ml is about 20–30%, unnecessary biopsies are performed with a high ratio, particularly in this group.[1,2] This causes additional morbidity and anxiety in patients. Many factors such as benign prostate hypertrophy or interventions on the prostate cause increase in PSA values.

Although it is known that acute prostatitis increases PSA, its relation to prostatic inflammation unrelated to clinical prostatitis is controversial in the literature.[4,5,12] However, many studies have shown that inflammation is a factor that must be considered in prostate cancer screening studies, as it increases PSA values.[5,6,10,13]

In 1995, Nadler *et al*.[5] found in their series, in which they compared 147 patients without clinical prostatitis and with high PSA values to 64 patients with normal PSA values, that acute and chronic prostatitis was related to the increase in PSA. In 1997, Irani *et al*.[7] separately classified the spreading level and aggressiveness of prostatic inflammation, and stated that PSA increase was affected not by the grade of inflammation extent, but that it was affected by the aggressiveness indicating the level of impairment in the epithelial structure. There are many studies in the literature that support and do not support this finding.[10,12,13]

When it is considered that prostate inflammation can be focal or diffuse, and that PSA increase is related to the aggressiveness rather than the amount of inflammation,[7] it can be foreseen that there is inflammation in a focus independent from the inflammation finding in EPS. Therefore, PSA changes were examined in our study in both EPS (+) and (−) patients with antibiotic therapy, and no differences were found between these two groups.

Inflammation in biopsy with similar ratios in EPS (+) and (–) patient groups renders the sensitivity of EPS in demonstrating inflammation questionable. Larger series are required with patients not receiving antibiotic therapy in order to have an idea on this subject.

Similar PSA changing in patients with positive culture can be related to the anti-inflammatory effect of antibiotic therapy. A study with a control group is needed in order to clearly establish this issue.

Prostate cancer was found in 10.8% of the patients with PSA between 4 and 10 ng/ml. The prostate cancer ratio in patients without suspicious findings in DRE and PSA values between 4 and 10 ng/ml is reported to be around 20% in the literature.[1,2] The reason for the smaller value for this ratio can be the rejection of re-biopsy by one patient in whom a focus of atypical glands was determined in the biopsy, and the forming of our patient group mostly from individuals applying to the outpatient clinic with lower urinary system complaints. Together with this, prostate cancer was found in none of the 10 patients with PSA values below 4 ng/ml. This was consistent with the study of Karazanashvilii and Managadze[9] Although it appears significant that prostate cancer was found in only 6.6% of the patients with decreased PSA over 4 ng/ml, together with the fact that prostate cancer was seen in patients with elevated PSA with a ratio of 29%, finding prostate cancer in a small number of patients in our study prevents us from making a more definite conclusion. We believe that studies in larger series are required.

Although in the literature it has been reported that PSA decreases below 4 ng/ml following antibiotic therapy in 43.1–60% of the patients with inflammation findings in EPS or in urine after massage, and PSA values remaining over 4 ng/ml is accepted as the criterion for making a biopsy, it has been suggested that biopsy can be avoided only in 18.8–32.1% of all patients.[8,9,23] In our study, however, nine patients out of 18 in whom PSA values decreased below 4 ng/ml had negative EPS. In this case, if the threshold value for biopsy is taken as 4 ng/ml, biopsy could be avoided only in 18.8% of all the patients if antibiotic therapy was given to only EPS (+) patients. However, we can avoid biopsy in another 18.8% if we give antibiotic therapy also to EPS (−) patients. With these findings, it can be suggested that biopsy can

be avoided in 37.5% of all patients by giving antibiotic therapy in both groups.

The effect of inflammation on the per cent-free PSA is controversial in biopsy-based studies; there are reports stating that inflammation does not change it as well as reports stating reduction.[6,14–16] Since Jung *et al*. have reported that fPSA ratio in patients with prostatitis is smaller than in patients with benign hyperplasia,[16] prostatitis therapy is expected to raise this ratio. Consistent with this expectation, per cent-free PSA significantly increased after antibiotic therapy in our study.

Requiring the use of a different antibiotic in only one patient according to the secretion or urine culture after massage indicates the needlessness of this examination in every patient. However, it has been reported in the literature that Gram-positive *Enterococci*, *Corynebacterium* family, *Clamidia trachomatis* and *Uroplasma uroliticum* can be found in many patients as well as Gram-negative bacteria.[17–20] However, again according to the literature, clinical success and microbiological eradication reaching 75% can be achieved with quinolone group antibiotic therapy in bacterial chronic prostatitis.[21] Therefore, although studies on larger series are required, starting directly with quinolone group antibiotics appears to be a good alternative.

Whereas performing EPS in all the patients and continuing with culture in positive patients increase the cost, it changed the antibiotic selection in only one patient. Therefore, prostatic massage does not appear to be necessary in all patients, and starting antibiotic therapy directly appears to be a good alternative. Performing biopsies in patients with PSA values over 4 ng/ml after an antibiotic therapy for 3 weeks with the quinolone group can be beneficial in terms of cost, as well as avoiding morbidity when compared to performing a biopsy directly.

Conclusions

As a result, we suggest an antibiotic therapy for 3 weeks in all patients when PSA is in the gray zone and DRE is normal without regarding EPS before biopsy, and making a decision for biopsy according to the PSA control 3 weeks later.

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