RESEARCH ARTICLE

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Investigation of the Relationship of Two-Glass Test with Prostate Biopsy and Presence and Grade of Asymptomatic Prostate Inflammation in Men with Serum Prostate-Specific Antigen Level Between 2.5-10 ng/ml

ABSTRACT

Objective: Prostate-specific antigen (PSA) is utilized as a marker to detect prostate cancer. Elevated PSA levels often lead to prostate biopsy to assess the potential presence of cancer. However, PSA elevation is not specific to cancer and can be caused by various conditions, including benign prostatic hyperplasia (BPH), urinary tract infections, and chronic prostatitis. Notably, approximately 66% of patients undergoing biopsy do not have prostate cancer, leading to unnecessary procedures and associated complications. Chronic prostatitis is detected in around 40% of these biopsies. The two-glass test involves examining urine before and after a rectal examination to diagnose chronic prostatitis. This study aims to investigate the effectiveness of the two-glass test in predicting prostatitis and inflammation in patients with PSA levels between 2.5-10 ng/ml who have undergone prostate needle biopsy.

Materials and Methods: The study included fifty-two male patients aged between 50 and 78 years with PSA levels between 2.5 and 10 ng/ml who presented to our clinic. All patients underwent the EPS-two-glass test and prostate biopsy. EPS (expressed prostatic secretion) is obtained by collecting fluid from the urethra after prostate massage, while VB-3 (voided bladder-3) is urine collected after a massage. These samples are used to detect prostate infection. Prostate inflammation was deemed significant if ≥10 leukocytes were observed under the microscope. Patients were categorized into three groups based on pathology results: prostate cancer, BPH, and chronic prostatitis. The chronic prostatitis group was further classified based on histopathological calcification described by Nickel.

Results: Chronic prostatitis was detected in 38% of the study participants. VB3 positivity was significantly higher in the chronic prostatitis group compared to the other groups (p = 0.028). Although no significant difference was observed in the prevalence of inflammation and PSA elevation, PSA levels were higher in the multifocal inflammation subgroup compared to the focal inflammation group.

Conclusions: The relationship between chronic prostatitis and PSA elevation remains unclear. Although this study did not find a statistical relationship between inflammation and PSA elevation, the significant correlation between chronic prostatitis and VB3 positivity suggests a potential link. These findings can serve as a foundation for further research aimed at reducing unnecessary biopsies.

Keywords: PSA Elevation, Prostate Cancer, Chronic Prostatitis, Two Glass Test.

Serum Prostat-Spesifik Antijen Düzeyi 2,5-10 ng/ml Arasındaki Erkeklerde İki Kadeh Testinin Prostat Biyopsisi Ve Asemptomatik Prostat İnflamasyonu Varlığı ve Derecesiyle İlişkisinin Araştırılması

ÖZET

Amaç: Prostat spesifik antijen (PSA), prostat kanserini tespit etmek için kullanılan bir belirteçtir. Yüksek PSA değerlerinin tespit edilmesi durumunda, prostat kanseri olasılığı göz önünde bulundurularak prostat biyopsisi yapılır. PSA yükselmesi prostat kanserine özgü olmayabilir, aynı zamanda benign prostat hiperplazisi (BPH), idrar yolu enfeksiyonu ve kronik prostatit gibi durumlar da neden olabilir. Biyopsiye giren hastaların yaklaşık %66'sında prostat kanseri tespit edilmez ve hastalar gereksiz biyopsi ve biyopsi komplikasyonlarına maruz kalırlar. Bu biyopsilerin yaklaşık %40'ında kronik prostatit tespit edilir. İki bardak testi, kronik prostatiti teşhis etmede kullanılan rektal muayene öncesi ve sonrası idrarın incelenmesine dayanır. Bu çalışmada, 2,5-10 ng/ml arasında PSA değerine sahip ve prostat iğne biyopsisi yapılan hastalarda iki bardak testinin prostatit ve inflamasyon insidansını tahmin etmedeki etkinliğini ortaya çıkarmayı amaçladık.

Gereç ve Yöntem: Kliniğimize başvuran, yaşları 50 ile 78 arasında değişen, PSA değerleri 2,5 ile 10 ng/ml arasında olan elli iki erkek hasta çalışmaya dahil edildi. Tüm hastalara EPS-iki bardak testi ve prostat biyopsisi uygulandı. EPS; prostat masajı yapıldıktan sonra üretradan sıvı alınarak elde edilen bir örnektir; VB-3; masaj sonrası boşaltılan yaklaşık 10 ml idrarı gösterir. EPS ve VB3 prostat enfeksiyonunu tespit eder. Mikroskop altında ≥10 lökosit, prostat inflamasyonu için anlamlı kabul edildi. Patoloji sonuçlarına göre, hastalar üç gruba ayrıldı; prostat kanseri, BPH ve kronik prostatit. Kronik prostatit grubu, Nickel tarafından tanımlanan histopatolojik kalsifikasyona göre sınıflandırıldı.

Bulgular: Bu çalışmada, kronik prostatit oranının %38 olduğu bulundu. VB3 pozitifliği, kronik prostatit grubunda diğer gruplara göre istatistiksel olarak önemli bulundu (p = 0,028). İnflamasyon prevalansı ile PSA yükselmesi arasında istatistiksel olarak anlamlı bir fark bulunmamakla birlikte, PSA, multifokal inflamasyon alt grubunda, odaklı inflamasyon hastalar grubundan daha yüksek bulundu.

Sonuç: Kronik prostatit ile PSA yükselmesi arasındaki ilişki hala belirsizdir. Bu çalışmada, inflamasyon ile PSA yükselmesi arasında istatistiksel bir ilişki bulunmamış olmasına rağmen, kronik prostatit ile VB3 pozitifliği arasındaki önemli korelasyon, bu ilişkinin olasılığını güçlendirmektedir. Bu bulgular, gereksiz biyopsileri önlemeye yönelik ileri çalışmaların temeli olabilir.

Anahtar Kelimeler: PSA Yüksekliği, Prostat Kanseri, Kronik Prostatit, İki Kadeh Testi.

INTRODUCTION

Prostate-specific antigen (PSA) is a commonly used marker for detecting and monitoring prostate cancer (1,2). However, PSA levels can also be elevated in various physiological events and benign conditions, leading to challenges in its specificity for cancer detection. Procedures such as prostate massage, transrectal ultrasonography (TRUS), and biopsy can temporarily increase PSA levels (3-5). While additional tests like the free PSA/total PSA ratio, PSA density, and Multiparametric Prostate Magnetic Resonance Imaging (MpMRI) have been used to enhance PSA test specificity, rates of unnecessary biopsies remain high (6). Spontaneous fluctuations in PSA levels without apparent cause are considered a potential cause of false-positive results. However, the relationship between the magnitude of these fluctuations and prostate histology is not well understood. The association between serum PSA levels and subclinical prostatic inflammation is also unclear. Elevated PSA levels in patients with negative biopsy results present a challenge for clinicians in explaining the PSA elevation in prostate cancer screening (7,8).

Inflammation may be present in up to 42% of patients undergoing prostate biopsy (7). High serum PSA levels are often linked to prostate inflammation, contributing to false-positive PSA tests. However, there is limited guidance on how to address this inflammation-related confusion when deciding on biopsy. Besides non-malignant conditions, benign prostatic hyperplasia (BPH) and prostatitis have been reported to contribute to PSA elevation. Studies investigating the relationship between PSA levels and asymptomatic prostatic inflammation based on morphological parameters have yielded conflicting results.

Current knowledge about prostatic inflammation in biopsies primarily stems from retrospective studies. Our study aimed to assess the frequency of asymptomatic prostatitis in prostate needle biopsy specimens from men with PSA levels between 2.5-10 ng/ml and evaluate the predictive value of the two-glass test for detecting this inflammation.

Prostate-specific antigen (PSA) is a widely used marker in the detection and follow-up

of prostate cancer (1,2). PSA is not specific to cancer; its level can be elevated in many physiological events and benign conditions (3,4,5). Various urological manipulations, prostate massage, transrectal ultrasonography (TRUS), and biopsy cause a temporary increase in serum PSA value. Although some auxiliary applications such as free PSA/total PSA ratio, PSA density, and Multiparametric Prostate Magnetic Resonance (MpMRI) imaging, which have been popular in recent years, are used to increase the specificity of the PSA test, unnecessary biopsy rates are still high (6). Many researchers consider spontaneous changes in the PSA level that occur for no apparent reason as one of the causes of false positive results. However, the relationship between the magnitude of spontaneous fluctuations in PSA value and prostate histology is not yet well known. The relationship between serum PSA value and subclinical prostatic inflammation is still unclear. Elevated PSA levels and negative biopsy results in patients with abnormal rectal examination make it difficult for clinicians to explain this increase in prostate cancer screening (7,8). Inflammation may be present in 42% of patients undergoing prostate biopsy (7). In most patients, high serum PSA levels are associated with prostate inflammation, which is considered one reason for false positive PSA testing. There is not enough information about how to eliminate this confusion caused by inflammation when making a biopsy decision. Apart from non-malignant conditions, BPH (1) and prostatitis have been reported to contribute to PSA elevation (4,7). Many studies have based the relationship between PSA value and asymptomatic prostatic inflammation on morphological parameters (1-3). These gave contradictory results.

Current information on prostatic inflammation in biopsy is largely based on retrospective studies (9). Our aim in this study was to investigate the frequency of asymptomatic prostatitis in prostate needle biopsy specimens in men with a PSA value between 2.5-10 ng/ml and the predictive power of the two-glass test for this inflammation.

MATERIAL AND METHODS

Between June 2004 and August 2005, patients presenting to the urology outpatient clinic with lower urinary tract complaints and serum PSA values between 2.5 and 10 were eligible for inclusion in the study. The study received approval from the ethics committee. All patients underwent a series of tests, including rectal examination, full urine examination, urine culture, expressed prostatic secretion (EPS), and the two-glass test. EPS, obtained by collecting fluid from the urethra after a prostate massage, and VB-3 in the two-glass test, referring to the first 10 ml urine sample after prostate massage, were analyzed. Additionally, 8-quadrant prostate biopsy and prostate volume measurement were performed under TRUS guidance.

Patients were excluded from the study if they:

1) Had symptoms of prostatitis
2) Had a PSA value less than 2.5ng/ml or more than 10ng/ml
3) Had a history of prostate-related surgery
4) Used drugs that affect PSA
5) Had a history of rectal ultrasound probe insertion
6) Had a urinary tract infection

Urine samples were collected before and after prostate massage, centrifuged, and the amount

of leukocytes in the sediment was measured. Prostate inflammation was considered significant if it was ≥10 leukocytes at high magnification under the microscope. PSA levels and prostate volumes were determined by transrectal ultrasound. All patients underwent 8-quadrant 18 auge needle fine aspiration biopsy. Patients diagnosed with chronic prostatitis in the biopsy sample were classified according to the histopathological classification of chronic prostatitis specified by Nickel (Tables 1a, 1b, and 1c) based on localization, extent, and degree. Thirteen out of 65 initially included patients were excluded based on the exclusion criteria, leaving 52 patients for the study.

Table 1a. Classification according to localization and histological features.

Anatomical Localization	Histological Pattern
Glandular	Inflammatory content in the duct or epithelium and/or in the lumen
Peri glandular	Inflammatory content in the stroma gland and distance to the channels is within 50μm
Stromal	The inflammatory content is in the stroma, and the gland and the distance to the channels are 50μm further.

Table 1b. Classification according to spread and area invaded by inflammatory cells.

According to the spread	Area invaded by inflammatory cells
focal	less than 10%
multifocal	10-50%
Widespread	more than 50%

Table 1c. Classification according to grade and morphology

Grade (degree)	Morphological description (inflammatory cell density, cell/mm²)
1/light	Inflammatory cells separated by distinct spaces (< 100)
2/medium	Tissue destruction and inflammatory cell clusters without lymphoid nodules. (100-500)
3/severe	Tissue destruction and inflammation cell clusters with lymphoid nodules (>500)

Statistical Analysis: The statistical analysis of the study was performed using the SPSS (Statistical Package for Social Sciences) version 10.0 for Windows. Student's t-test and One-way ANOVA test were employed to compare numerical data, in addition to descriptive statistical methods. Kruskal-Wallis and Mann-Whitney U tests were utilized for comparing groups with different distributions. The chi-square test was applied for the qualitative comparison of groups. The data were considered statistically significant at a 95% confidence interval with $p<0.05$.

RESULTS

The mean age of the cases was 65 ± 7 years. There was no statistically significant difference between the groups in terms of patient age, total PSA, free PSA levels, PSAD, f/tpsa prostate volume and postvoid residual amount ($p>0.05$).

Considering the VB3 positivity rates (Table 2 and Figure 1), the elevation in the chronic prostatitis group was statistically significant compared to the other groups.

Table 2. Table of VB3 positivity in group

		Chronic Prostatitis	BPH	Prostate Cancer	p
		%	% (n)	% (n)	
VB3	+	40.0 (8)	5.0 (1)	20.0 (2)	*0.028
	-	60.0 (12)	95.0 (19)	80.0 (8)	

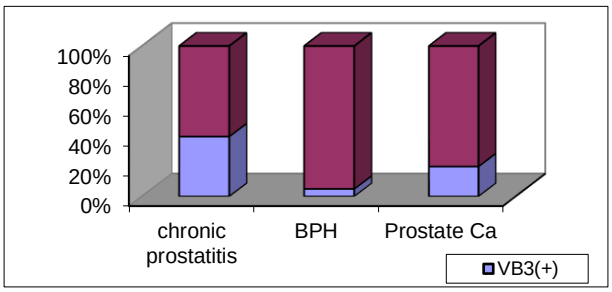

Figure 1. VB3 distribution by groups.

The mean age of the cases with a PSA value ≤4 was significantly lower than that of the cases with a PSA level of >4. No significant difference was found between prostate volume and PSA levels ($p>0.05$). Also, there is no statistically significant difference between PSA and histopathologic classification in the chronic prostatitis group (Table 3). According to VB3 positivity, no statistically significant difference was found between the mean PSA levels of the cases, the distribution of

inflammation localization, and the spread of inflammation (p>0.05) (Table 4). There is no statistically significant relationship between the prevalence of inflammation, localization of inflammation, grade of inflammation and age groups, PV level, and PSA level (p>0.05) (Table 5).

Table 3. Comparison of PSA level with histopathologic classification in the chronic prostatitis group.

		PSA				*p*
		≤ 4		> 4		
		Mean±SD	Median	Mean±SD	Median	
Age		58.00±7.35	56.5	67.06±6.83	67.5	***p:0.033****
Prostate Volume (PV)		42.50±7.32	40.5	66.56±44.67	60.5	***p:0.185***
		N	**%**	**n**	**%**	
Localization of inflammation	**stromal**	2	50.0	4	28.6	***p:0.569***
	glandular+ periglandular	2	50.0	10	71.4	
Prevalence of inflammation	**focal**	3	75.0	5	35.7	***p:0.275***
	multifocal	one	25.0	9	64.3	
Grade	**I**	2	50.0	6	42.9	***p:1.000***
	II+III	2	50.0	8	57.1	

Table 4. Table showing the comparison of chronic prostatitis features and VB3 results

		VB3				*p*
		+		-		
		Mean±SD	Media	Mean±SD	Media	
PSA		6.54±1.82	5.72	5.88±1.97	5.80	***0.32***
		n	**%**	**n**	**%**	
Localization of Inflammation	**stromal**	2	33.3	4	33.3	***1.00***
	glandular+ periglandular	4	66.7	8	66.7	
Prevalence of Inflammation	**focal**	1	16.7	7	58.3	***0.152***
	multifocal	5	83.3	5	41.7	
Grade of Inflammation	**I**	2	33.3	6	50.0	***0.638***
	II+III	4	66.7	6	50.0	

Table 5. Patient characteristics according to the prevalance, localization and the grade of inflammation

		Prevalence of Inflammation			Localization of Inflammation			*Grade of Inflammation*		
		Focal	Multifocal	*p*	Stromal	Glandular+ Periglandular	*p*	I	II+III	*p*
		%	%		%	%		%	%	
Age	**< 60**	37.5	10.0	***p:0.275***	16.7	25.0	***p:1.000***	25.0	20.0	***p:1.000***
	≥ 60	62.5	90.0		83.3	75.0		75.0	80.0	
PV	**<50**	62.5	40.0	***p:0.637***	16.7	66.7	***p:0.131***	50.0	50.0	***p:1.000***
	> 50	37.5	60.0		83.3	33.3		50.0	50.0	
PSA	**≤ 4**	37.5	10.0	***p:0.275***	33.3	16.7	***p:0.569***	25.0	20.0	***p:1.000***
	> 4	62.5	90.0		66.7	83.3		75.0	80.0	

While there was no statistically significant difference in serum PSA mean and PSA density between cases with stromal inflammation localization, the FPSA ratio was found to be at a statistically significant level (p<0.05). (Table 6)

Table 6. Comparison of serum PSA, PSA density and FPSA percentage by inflammation localization

	Inflammation Localization				*p*
	Stromal		Glandular+ Periglandular		
	Mean±S	Median	Mean±S	Median	
Serum PSA	5.82±2.5	5.59	5.74±1.76	5.52	***p:1.000***
PSA Density	0.09±0.0	0.08	0.13±0.08	0.11	***p:0.779***
FPSA rate	26.11±9.6	25.19	17.98±6.48	18.84	***p:0.039****

DISCUSSION

Asymptomatic prostate inflammation is considered one of the subgroups of chronic prostatitis, typically diagnosed through EPS/glass test or histopathological evaluation. While PSA measurement is crucial for early prostate cancer diagnosis, its sensitivity and specificity are limited. In asymptomatic patients with high PSA values, approximately 50% of cases might be attributed to prostatitis, as detectable after TRUS biopsy, suggesting a potential association between high

PSA values and inflammation (11,12). However, some studies argue against a significant increase in PSA levels due to chronic prostatitis (13,14). In our study, we observed a prostatitis rate of 38% post-prostate biopsy, consistent with reported rates in the literature ranging from 5-98% in various biopsy methods and autopsy specimens (15,16). Brawn et al. reported chronic prostatitis in 50% of 105 autopsy samples in their study (17).

A notable finding in our study was the significantly higher VB3 positivity in the chronic prostatitis group compared to other groups ($p = 0.028$). In one study, VB3 positivity was detected in 92% of those with positive EPS results. Of the 180 patients who had less than 10 leukocytes in EPS, 178 of them also had less than 10 leukocytes in the VB3 test (18). This indicates that VB3, which can be easily obtained from all patients, could potentially replace EPS, which is sometimes unavailable. Lee et al. reported a 20.7% prostate cancer detection rate in patients with negative EPS or VB3 tests, suggesting a potential role for these tests in identifying patients at higher risk for prostate cancer (19). Additionally, in a systematic review, antibiotic treatment normalized PSA levels in a significant number of patients with positive VB3 or EPS tests, indicating a potential benefit of antibiotic therapy with quinolone treatment in symptomatic VB3-positive patients (20).

While some studies have found a positive correlation between prostate volume and PSA levels, we did not observe a significant relationship in our study. The discrepancy may be due to differences in sample size, prostate volume variability, and the PSA range studied. Notably, both our study and another study of Kwak et.al observed a positive correlation between inflammation extent and prostate volume, suggesting a potential link between prostate inflammation and hyperplasia (21). While multifocal inflammation was 60% in those with PV >50cc, it was found around 40% in those with <50cc in our study.

No significant relationships were found between age groups, prostate volume, PSA levels, and inflammation localization in our study. However, glandular and peri-glandular inflammation predominated in prostates below 50cc, while stromal inflammation was more prominent in larger prostates (>50cc), reflecting the shift in glandular to stromal tissue ratio with increasing prostate size. This finding warrants further investigation. In the study of Nadler et al., it was noted that both acute and chronic inflammation caused an increase in PSA. They reported acute inflammation in 63% of patients with elevated PSA and 27% of patients with normal PSA. For chronic inflammation, these values are 99% and 77%, respectively ($p = 0.05$) (22). Neal found an increase in PSA after acute inflammation induction in his study in monkeys and noted that PSA decreased to its normal value with its treatment (7). Although it has been shown in many studies that BPH increases PSA levels, this was not taken into account in some studies advocating the relationship between PSA elevation and chronic inflammation (23,24).

Biopsying patients with high PSA levels but negative for cancer does not definitively rule out undetected microscopic prostate cancer. Chronic inflammation may occur in atrophic glandular areas, where PSA production is diminished, potentially masking inflammation. Studies have presented conflicting findings regarding the correlation between inflammation and PSA levels (25). The free-to-total PSA ratio (f/tPSA) is significantly higher in stromal inflammation compared to other regions ($p = 0.039$). This elevation may be due to the breakdown of the anatomical and physiological barrier between the prostate and blood vessels in the stromal region, which is rich in blood vessels. Moon's study, which infected the human prostate carcinoma cell line LNCaP with in vitro bacteria, did not find an increase in PSA levels (26). This result supports the hypothesis that infection and inflammation may facilitate the diffusion of PSA into the blood by affecting natural physiological and anatomical barriers.

In our study, we observed a relationship between the spread of inflammation and PSA elevation, although it was not statistically significant. The mean PSA was higher in the multifocal inflammation subgroup compared to the focal inflammation group.

These findings suggest that while inflammation and PSA levels may be related, the exact nature of this relationship and its clinical implications require further investigation.

The most important limitation is the limited number of patients. Further multicentre study should be carried out to establish a more accurate model. Another limiting factor is that the prostate biopsy was performed in 8 quadrants instead of 12 quadrants. In conclusion, our study contributes to the understanding of asymptomatic chronic prostatitis and its relationship with PSA elevation. While we did not find a statistical association between inflammation and PSA elevation, we observed a significant correlation between chronic prostatitis and VB3 positivity. These findings suggest a potential role for VB3 in identifying patients at higher risk for prostate cancer and highlight the need for further multicenter studies to establish more accurate models.

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