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Is thiol/disulphide homeostasis reliable as an additional serum marker to PSA in the diagnosis of prostate cancer?

Prostat kanseri tanısında thiol/disülfid dengesi PSA'ya ek bir serum belirteç olarak güvenilir midir?

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ABSTRACT

Aim: We aimed to investigate thiol/disulphide homeostasis as an additional serum marker to prostate specific antigen (PSA) in the diagnosis of prostate cancer.
Patients and Methods: Prospective study was conducted among 174 patients with PSA levels of 2.5–20 ng/mL without suspicion of malignancy in rectal examination and who underwent prostate needle biopsy. A total of 75 patients were included in our study after exclusion criteria. Serum PSA, thiol, and disulphide levels of the patients were recorded prior to biopsy. In this study, 25 patients with pathology results indicating prostate cancer, 25 randomly selected patients with pathology results indicating chronic prostatitis, and 25 randomly selected patients with pathology results indicating benign prostate hyperplasia (BPH) were included.
Results: Total and native thiol levels were higher in prostate cancer group than in BPH and chronic prostatitis groups; however, no statistically significant difference was observed (p> 0.05). When prostate cancer sub-groups were investigated, total and native thiol levels were noted to be higher in patients with a Gleason score of 7, 8, and 9 than in those with a Gleason score of 6; however, no statistically significant difference was observed (p> 0.05).
Conclusions: Thiol levels were higher in prostate cancer group than in benign disease (BPH and chronic prostatitis) groups; these levels were also higher in group with high Gleason scores (Gleason 7, 8, or 9) than in group with a low Gleason score (Gleason 6); however, these differences were not statistically significant.

Key words: Prostate cancer, Thiol, Disulphide, Diagnosis, Prostate specific antigen

ÖZ

Amaç: Bu çalışmada, prostat kanseri tanısında thiol/disülfid dengesinin prostat spesifik antijene (PSA) ek bir serum markırı olarak değerlendirmeyi amaçladık.
Hastalar ve Yöntemler: Prospektif çalışmamız PSA düzeyi 2.5-20 ng / mL olan, rektal muayenede malignite şüphesi olmayan ve prostat iğnesi biyopsisi yapılan toplam 174 hasta üzerinde yapıldı. Dışlama kriterleri sonrası çalışmamıza toplam 75 hasta dahil edildi. Biyopsi öncesi hastaların serum PSA, thiol ve disülfid düzeyleri kaydedildi. Çalışmamıza patoloji sonucu prostat kanseri olan 25 hasta, patoloji sonucu kronik prostatit olan 25 hasta ve patoloji sonucu benign prostat hiperplazisi (BPH) olan 25 hasta dahil edildi.
Bulgular: Prostat kanseri grubunda total ve native thiol seviyeleri BPH ve kronik prostatit gruplarından daha yüksekti; ancak, istatistiksel anlamlı bir farklılık gözlenmedi (p> 0.05). Prostat kanseri alt grupları incelendiğinde, total ve native thiol seviyelerinin Gleason skoru 7, 8 ve 9 olan hastalarda, Gleason skoru 6 olanlara göre daha yüksek olduğu saptandı; ancak, istatistiksel anlamlı bir fark gözlenmedi (p> 0.05).
Sonuç: Thiol seviyeleri prostat kanseri grubunda, benign hastalık (BPH ve kronik prostatit) gruplarından daha yüksekti; bu seviyeler aynı zamanda Gleason skoru yüksek olan grupta (Gleason 7, 8 veya 9), Gleason skoru düşük olan (Gleason 6) gruba göre daha yüksekti; ancak, bu farklılıklar istatistiksel olarak anlamlı değildi.

Anahtar Kelimeler: Prostat kanseri, Thiol, Disülfid, Tanı, Prostat spesifik antijen

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INTRODUCTION

Prostate cancer (PCa) is the most common cancer after skin cancers and accounts for the second-highest morbidity rate in men [1,2]. Tumor markers have been more frequently used in the diagnosis of PCa than in the diagnosis of other urological malignancies. The use of prostate-specific antigens (PSA) as tumor markers in prostate tumour has led to a rise in the diagnosis of non-palpable T1c stage PCa [3]. Contrarily, Stamey and colleagues demonstrated that elevated PSA levels were associated with advanced stage PCa, and further studies have supported this association [4-6]. Unnecessary biopsies and post-biopsy complications due to elevated PSA levels may pose an important problem. Conversely, diagnosis and treatment of clinically unimportant cancer on the basis of PSA screening results also puts the patients under risk of unwanted complications as well as surgical risk of radical prostatectomy. In addition to serum PSA level measurements, different practices have been developed for preventing unnecessary biopsies and detecting clinically significant PCa.

In 2014, Erel and colleagues defined thiol/disulphide homeostasis for the first time and showed its measurability in serum [7]. Thiols form covalent disulphide bonds with oxidants during tissue oxidation. These disulphide bonds can be reduced back to the thiols, resulting in the formation of a dynamic thiol/disulphide homeostasis, which plays a very important role in antioxidation, and, therefore, it is believed to play a role in the pathogenesis of numerous diseases such as diabetes, coronary artery disease, and cancer [8-10]. In the present study, thiol/disulphide homeostasis was evaluated as an additional marker to PSA in the diagnosis of PCa in our tertiary referral center.

PATİENTS AND METHODS

The study was prospectively conducted in patients who applied to urology outpatient clinic between March 2017 and January 2018 and who were scheduled for prostate biopsy due to elevated PSA levels after receiving written informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all the patients

Blood samples were collected from all patients prior to biopsy for evaluation of serum thiol and disulphide levels. Among 174 patients with PSA levels of 2.5–20 ng/mL without suspicion of malignancy in rectal examination and who underwent prostate needle biopsy, 25 patients with pathology results indicating prostate adenocarcinoma, 25 randomly selected patients from the remaining patients with pathology results indicating chronic prostatitis (CP), and 25 randomly selected patients with pathology results indicating BPH were included in this study. Patients with a history of long-term urethral catheterization, a urinary tract infection, a history of uncorrected coagulopathy, a myeloproliferative disease, or PCa with metastases detected in imaging procedures were excluded from this study. Single-dose antibiotic prophylaxis (ciprofloxacin 500 mg 1x1) and distal gastrointestinal system cleaning (rectal enema 135 cc) were applied to all patients one hour before the biopsy. After transrectal ultrasound examination, prostate biopsy was performed on all 12 quadrants of prostate under intrarectal local anesthesia (lidocain 5-10 ml %10) with a 25 cm 18 Gauge Tru-Cut needle powered by an automatic spring-loaded disposable biopsy gun. All procedures were applied in outpatient settings and the antibiotic prophylaxis was continued for additional three days. After biopsy, all specimens were examined by a same uro-pathologist. Serum PSA, thiol, and disulphide levels of the patients were enrolled prior to biopsy.

Statistical analysis

Statistical Package for the Social Sciences version 22 (SPSS Inc.; Chicago, IL, USA) software package program was used for all statistical analyses while evaluating the findings obtained in this study. The normal distribution of the parameters was analyzed using Shapiro–Wilk test. In addition to descriptive statistics (mean and standard deviation), one-way ANOVA was used for the inter-group comparison of quantitative parameters that were normally distributed, and Tukey's HSD test was used for identifying the group that caused the difference. Student's t-test was used for comparing normally distributed parameters between the two groups. $P < 0.05$ was considered statistically significant.

RESULTS

The study included 75 men with the mean age were 62.88 ± 7.91 years (range, 42 and 78 years). PSA levels ranged from 2.7 to 19.9 ng/mL, with a mean of 9.41 ± 4.64 ng/mL. Prostate volume ranged from 24 to 152 mL, with a mean of 66.97 ± 23.75mL.

Among the prostate biopsy groups, total thiol and native thiol levels were higher in the PCa group than in the benign disease (BPH and CP) groups; however, no significant difference in terms of mean native thiol, total thiol, and disulphide levels (P > 0.05) was observed (Table 1).

Table 1. Evaluation of thiol, disluphide and IMA values between prostate biopsy groups

	Prostate Biopsy Groups			
	BPH (N=25)	Chronic prostatitis (N=25)	Prostate cancer (N=25)	p
	Mean±SD	Mean±SD	Mean±SD	
Native Thiol	202,98±51,09	184,95±76,71	211,28±81,39	0,408
Total Thiol	233,23±59,63	208,83±79,85	240,01±94,49	0,346
Disulphide	15,1±6,04	11,92±5,27	14,32±7,78	0,202
IMA	0,82±0,18	0,96±0,23	0,89±0,19	0,041*

A significant difference was noted among the prostate biopsy groups in terms of mean ischemia modified albumin (IMA) levels (P = 0.041). Findings of paired comparison test conducted for determining the source of difference revealed that mean IMA levels were significantly lower in BPH group than in CP group (P = 0.031). No difference was noted between the other prostate biopsy groups in terms of mean IMA levels (P > 0.05) (Table 1).

No difference was noted between the malignant and benign disease groups in terms of native thiol, total thiol, disulphide, and IMA levels (P > 0.05) (Table 2).

When PCa sub-groups were investigated, total thiol and native thiol levels were noted to be higher in patients with a Gleason scores of 7, 8, and 9 than in those with a Gleason score of 6; however, no significant difference in terms of native thiol, total thiol, disulphide, and IMA levels (P > 0.05) was observed (Table 3).

Table 2: Evaluation of thiol, disulphide and IMA values between malignant and benign groups

	Prostate Biopsy Groups		
	BPH+ Chronic prostatitis (N=50)	Prostate cancer (N=25)	P
	Mean±SD	Mean±SD	
Native Thiol	193,95±65,15	211,28±81,39	0,317
Total Thiol	221,03±70,83	240,01±94,49	0,327
Disulphide	13,51±5,83	14,32±7,78	0,645
IMA	0,89±0,22	0,89±0,19	0,994

Student t Test IMA: Ischemia modified albumin, BPH: Benign prostate hyperplasia

Table 3. Evaluation of Thiol, disluphide and IMA values among pathology groups according to Gleason score in patients with prostate cancer

	Prostate Cancer Pathology		
	Prostate Cancer Pathology	Prostate cancer (N=25)	P
	Gleason 6 (n=10)	Gleason 7-8-9 (n=15)	
Native Thiol	Mean±SD	Mean±SD	0,775
Total Thiol	235,54±66,29	242,8±110,55	0,853
Disulphide	15,1±7,7	13,83±8,04	0,693
IMA	0,91±0,15	0,88±0,22	0,674

1.Student t Test *p<0.05 IMA: Ischemia modified albumin

DISCUSSION

The introduction of PSA in the screening and diagnosis of PCa has markedly increased the diagnosis rate of PCa. However, prospective studies comprising large series with long-term follow-up have demonstrated that quality of life decreased owing to over-diagnosis, over-treatment, and related complications with an increase in diagnosis rate of clinically insignificant PCa [11-16]. Furthermore, unnecessary biopsies, treatment and related complications caused cost-effectiveness. In a study, 76,693 men aged between 55 and 74 years were separated into two groups and annual serum PSA levels were measured in the screening group [17]. In this study, authors carried out prostate biopsy on individuals with PSA levels of more than 4 ng/mL and/or positive findings in rectal examination. No significant difference was noted in PCa mortality rate between the screening and control groups [17]. In ERSPC study, 162,243 men from seven European countries aged between 55 and 69 years were included, and screening and control groups were followed up for 9 years [15]. This study reported a 20% decrease in PCa mortality rate using PSA-based screening. It also reported

by many other authors that 48 patients had to be treated and 1410 patients had to be screened for preventing a single mortality from PCa and that PSA screening was associated with a high risk of over-diagnosis [11-18]. For 11- and 13-year follow-ups, decrease in mortality rate was 21% and 29%, number of men to be screened was 1055 and 781, and number of patients to be treated was 37 and 27, respectively [11-18].

Taking the above-mentioned information into consideration, urologists require alternative new markers and methods, such as free PSA/total PSA ratio, prostate cancer antigen-3, prostate health index, PSA velocity, 4K score and PSA doubling time, to complement PSA for detecting and managing patients with clinically significant PCa. In addition, multiparametric magnetic resonance imaging, an imaging technique that has been increasingly used in recent years and included in the urology guidelines, issued for performing biopsy on patients requiring the procedure and for effective active monitoring on patients during follow-ups. The use of Grade-Group classification in the diagnosis of PCa can facilitate the detection of clinically important PCa. In our presented study, the role of thiol/disulphide homeostasis was investigated for diagnosing PCa, which we consider to be as sensitive as, but more specific than, PSA.

In a recent study, authors investigated the role of thiol/disulphide homeostasis in the differentiation of benign diseases and PCa and found that total thiol and native thiol levels were significantly higher in patients with PCa than in those with benign diseases ($P < 0.001$) [19]. In our study, we found that total thiol and native thiol levels were higher in the PCa group than in the benign disease (BPH and CP) groups. We also determined that total thiol and native thiol levels were higher in patients with high Gleason scores (Gleason 7,8, or 9) than in those with a low Gleason score (Gleason 6). However, this difference was not statistically significant in this study ($P > 0.05$). In a study, the authors evaluated thiol/disulphide homeostasis prior to and 6 months following radical prostatectomy in patients with PCa and reported that elevated oxidative stress in these patients may cause metabolic disturbance and play a role in the etiology of PCa [20]. In a recent study, the authors investigated IMA levels and inflammatory biomarkers in patients with prostate tumour [21]. This study and control groups included 25 patients with PCa and 30 healthy individuals. According to this retrospective study, C reactive protein, IMA, and PSA levels were higher and free PSA and ferric reducing ability of plasma levels were lower in the PCa group than in the control group. The authors of this study indicated that both inflammatory and oxidative processes are increased during prostate tumour and there is a reduction of antioxidant defenses in prostate tumour pathology [21]. Taken together, elevated oxidative stress and inflammation were reportedly effective in the pathogenesis of PCa. Mastella and colleagues reported that IMA levels were significantly higher in patients with BPH [22]. In the present study, the mean IMA level was significantly lower in the BPH group than in the CP group, but no important difference was observed in the PCa group.

The limitations of our study include the absence of a control group of healthy individuals, small sample size, and the presence of comorbidities that may affect serum thiol/disulphide homeostasis in patients.

CONCLUSIONS

In PSA based PCa screening, certain complications, such as unnecessary biopsy, overdiagnosis, overtreatment, and a subsequent decrease in quality of life, can occur. Using a biomarker with high specificity in conjunction with PSA may aid in reducing frequency of these complications. The present study reported that total and native thiol levels were higher in the PCa group than in the benign disease (BPH and CP) groups; these levels were also higher in the group with high Gleason scores (Gleason 7, 8, or 9) than in the group with a low Gleason score (Gleason 6); however, these differences were not statistically significant. To achieve more accurate results about this new biomarker, randomized, greater number of patients and prospective studies are needed.

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