J Surg Med. 2021;5(6):615-619.
DOI: 10.28982/josam.867945

Research article

Journal of Surgery and Medicine
e-ISSN=2602-2079

Value of serum thiol/disulphide in chronic prostatitis

Halil Ferat Öncel [1], Remzi Salar [1], Engin Özbay [1], İbrahim Halil Dikici [2], Mehmet Demir [3], Ayhan Verit [4]

[1] University of Health Sciences, Medical Faculty, Mehmet Akif Inan Hospital, Department of Urology, Sanliurfa, Turkey
[2] University of Health Sciences, Medical Faculty, Mehmet Akif Inan Hospital, Department of Biochemistry, Sanliurfa, Turkey
[3] Harran University, Faculty of Medicine, Department of Urology, Sanliurfa, Turkey
[4] University of Health Sciences, Medical Faculty, Fatih Sultan Mehmet Hospital, Department of Urology, Istanbul, Turkey

ORCID ID of the author(s)

HFÖ: 0000-0003-4043-5597
RS: 0000-0002-5078-9367
EÖ: 0000-0001-7102-3064
İHD: 0000-0002-9427-5974
MD: 0000-0002-3618-0547
AV: 0000-0002-1602-9698

Corresponding Author
Halil Ferat Öncel
Department of Urology, University of Health Sciences, Medical Faculty, Mehmet Akif Inan Hospital, Esentepe Mah. Ertuğrul Cad. Sanliurfa, Turkey
E-mail: halilferat.oncel@gmail.com

Ethics Committee Approval
Ethics Committee of Harran University, date: 10.12.2018, number: HRU/10.12.18
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 June 20

Abstract

Background/Aim: Thiols are an important part of the antioxidant system which destroy reactive oxygen molecules, especially in inflammatory reactions. Maneuvers expressing the prostate fluid required for the diagnosis of chronic prostatitis are not practical and are rarely used in clinical practice. We aimed to compare the level of native thiol/disulphide as a supportive biomarker in patients with chronic abacterial prostatitis.

Methods: Twenty patients diagnosed with chronic prostatitis and 20 healthy volunteers were included in this prospective-case control study. Both groups were compared in terms of native thiol disulphide homeostasis, IPSS, QoL and PSA levels.

Results: In the chronic prostatitis group, the native thiol level was significantly lower (P=0.043), the % disulfide/natural thiol was higher (P=0.037), the international prostate symptom score was higher (P=0.006), the quality of life was higher (P=0.023) and the maximum flow rate was lower (P=0.009) compared to the healthy volunteers.

Conclusion: In this study, we found that the native thiol (SH) level in patients with chronic prostatitis was low and their disulphide level was high; therefore, we think that the level of native thiol/total thiol may assist in supporting the diagnosis of chronic prostatitis.

Keywords: Oxidative stress, Prostatitis, Quality of life, Reactive oxygen species, Thiol disulphide

How to cite: Öncel HF, Salar R, Özbay E, Dikici İH, Demir M, Verit A. Value of serum thiol/disulphide in chronic prostatitis. J Surg Med. 2021;5(6):615-619.

Introduction

The term prostatitis describes a wide range of inflammatory diseases from acute bacterial infection of the prostate to chronic pain syndromes, in which the prostate is inflamed. All these diseases seriously affect patients' quality of life and social life. The etiopathogenesis of prostatitis is not yet fully understood [1]. It is reported that the prevalence of prostatitis-like complaints or the diagnosis of prostatitis varies between 2 and 10% in the world [2]. Although chronic prostatitis is mostly known as a disease of the young, studies emphasize that men from any age group can be affected. Many studies were conducted on the relationship between oxidative stress and prostate cancer, benign prostatic hyperplasia (BPH), and prostate inflammation [3]. The incomplete understanding of the etiopathogenesis of chronic prostatitis causes difficulties in diagnosis and treatment. Although there were publications supporting the role of oxidative stress in etiopathogenesis, the number of these publications is limited.

Oxidative stress is a process in which the prooxidant-antioxidant balance in the body and tissues is disrupted. The occurrence of Reactive oxygen species (ROS), known as prooxidants, is a natural result of normal aerobic life. The presence and development of cells in oxygen-containing environments is not possible without powerful antioxidant and non-enzyme antioxidant systems. In aerobic life, continuously produced prooxidants need to be regularly absorbed and balanced by antioxidants; otherwise, oxidative damage occurs, which may lead to various pathologies [4]. Free oxygen radicals having a destructive effect, which are generated as a result of any extra or intracellular oxidative stress, are bound by thiols and inactivated. This reaction leads to the emergence of freeS-S bound molecules. Thiols are an important part of the antioxidant system in that they destroy reactive oxygen molecules and other free radicals produced by enzymatic and non-enzymatic pathways. Various methods are available to evaluate the effects of oxidative stress on the body, and for this purpose, different markers have been investigated. The automatic spectrophotometric analysis, an inexpensive, fast, and practical technique developed by Erel and Neselioğlu, is currently used to measure native thiol / disulphide bonds (SH/SS) homeostasis and allows for the specific measurements of SH and SS levels. The impairment of SH/SS homeostasis in favor of SS has been shown to affect disease pathogenesis. SH/SS homeostasis is impaired in cases such as cardiovascular diseases, diabetes mellitus, Parkinson's disease, chronic renal failure, liver disorders, rheumatic, and oncological diseases. While plasma SS levels are high in smokers, diabetes mellitus, obesity, pneumonia, multiple myeloma, bladder cancer, kidney cancer, and colon cancer patients, low levels of SS are found in patients with aggressive tumors [5].

Diagnosing chronic prostatitis is difficult and time-consuming in clinical practice. In addition, the lack of a marker used in diagnosis and follow-up is one of the main problems for the clinician. There are very few studies examining the relationship between isolated chronic prostatitis and thiol balance. In the current study, we aimed to compare the level of SH/SS as a supportive biomarker for diagnosis in patients with prostatitis classified in categories other than acute bacterial prostatitis (National Institutes of Health, Category I) and healthy individuals.

Materials and methods

Twenty patients who presented to the urology outpatient clinic of our hospital and were diagnosed with chronic prostatitis by four-glass test [2] between December 2018 and December 2019, and 20 healthy volunteers were included in the study. After obtaining detailed history and physical examination, the International Prostate Symptom Score (IPSS) and the Quality of life (QoL) Form, which measures quality of life according to urinary symptoms, were completed by all patients diagnosed with chronic prostatitis and healthy individuals. The Prostate specific antigen (PSA) level and the maximum flow rate (Q_{max}) values were also noted. The participants filled in the IPSS and QoL forms independently during the examination, with no interference. Uroflowmetry was performed at the third hour after oral hydration. Patients with a complaint of less than three months, those who received antibiotics or anti-inflammatory therapy within the last month, with a history of urethral or prostatic surgery, using pentoxifylline and vitamin preparations/antioxidants, and patients with diabetes mellitus, hypertension, a history of prostate cancer/malignancy, sleep apnea, and chronic kidney damage were excluded from the study. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. Prior to the study, approval was obtained from the Ethics Committee of Harran University Faculty of Medicine (date/number: 2018/18-12-15).

Sample collection and biochemical analysis

Venous blood samples were obtained from all participants after 12 hours of fasting and placed in tubes containing ethylenediaminetetraacetic acid, and the serum was immediately separated by centrifugation at 1,500 rpm for 10 minutes. The separated sera were kept at -80 °C after coding, and SH/SS homeostasis tests were conducted. SH/SS homeostasis was assayed using a new and automatic analysis technique found by Erel and Neşelioğlu [5]. The ratios of disulphide bonds / total thiol (SS/TT), SS/SH and SH/TT were calculated as percentages. The PSA and free PSA values were measured by the immunoassay method using an ARCHITECT i2000SR analyzer (Abbott Diagnostics).

Statistical analysis

Statistical Package for the Social Science for Windows program, version 24.0 was used to evaluate the data obtained in the research. The mean and standard deviation values for the parameters evaluated in the study were examined in all patients. The independent samples t-test was used to compare the test values of the patients with chronic prostatitis and the control group. Within the scope of the research, power analysis was performed to measure the adequacy of the sample size using G*Power program. For a d of 1.4352 and an actual power of 0.9548, the required sample size was 28 patients, 14 patients in each group. The fact that "d" which is the Cohen effect value, is above 0.80, shows that the study has a high effect level, and the statistical power of above 0.90 indicates that the sample size is sufficient [6-7].

Results

The mean ages of the patients with prostatitis and healthy volunteers were 41.55 (10.26) (27-69) years and 38.85 (12.6) (16-61) years, respectively (Table 1). There was no significant difference between the two groups in terms of age. The SH, TT, SS, %SH/TT, %SS/SH, %SS/TT and PSA levels of prostatitis patients were 329.4 (52.4) µmoL/L, 373.16 (59.0) µmoL/L, 21.88 (8.7) µmoL/L (Figure 1), 88.34 (3.8), 6.69 (2.38), 5.82 (1.9), and 1.19 (1.18) ng/ml, respectively. Their IPSS, QoL and Qmax were 7.3 (4.66), 0.75 (0.44) (Figure 2), and 14.65 (3.03) ml/sec, respectively.

Table 1: Comparison of the values between the chronic prostatitis and control groups

	Chronic prostatitis (n=20) Mean (SD) Min-Max	Control group (n=20) Mean (SD) Min-Max	t	*P*-value
Age	45.55(10.26) 27-69	38.85(12.6) 16-61	0.743	0.462
SH	329.4(52.4) 178.5-426.8	345.61(61.1) 155.5-429.5	-1,901	0.43*
TT	373.16(59) 207.9-437.3	384.9(67.76) 185.8-460.9	-1,586	0.561
SS	21.88(8.7) 5.25-36.05	19.66(8.89) 2.35-39.45	0.797	0.431
%SH/TT	88.34(3.8) 82.39-97.59	89.77(4.17) 82.88-98.72	-1.126	0.267
% SS/SH	6.69(2.38) 1.23-10.68	5.81(2.57) 0.64-10.32	2.121	0.37*
%SS/TT	5.82(1.9) 1.2-8.8	5.11(2.08) 0.63-8.55	1.126	0.267
IPSS	7.3(4.66) 1-16	4.05(1.7) 1-8	2.925	0.06**
QoL	1.4(1..4) 0-4	0.75(0.44) 0-1	2.371	0.23*
PSA	1.19(1.18) 0.4-6	1.07(0.85) 0.2-3.7	0.387	0.702
Qmax	14.65(3.03) 9-19	17.11(2.58) 11-22	-2.766	0.09**

Independent samples t-test, * $P<0.05$, ** $P<0.01$, SD: standard deviation, SH: native thiol, SS: disulfide, TT: total thiol, IPSS: International Prostate Symptom Score, QoL: Quality of Life Form, Q_{max}: maximum flow rate, PSA: prostate-specific antigen

Figure 1: Comparison of the native thiol, total thiol and disulfide levels of chronic prostatitis and control groups (in µmol units)

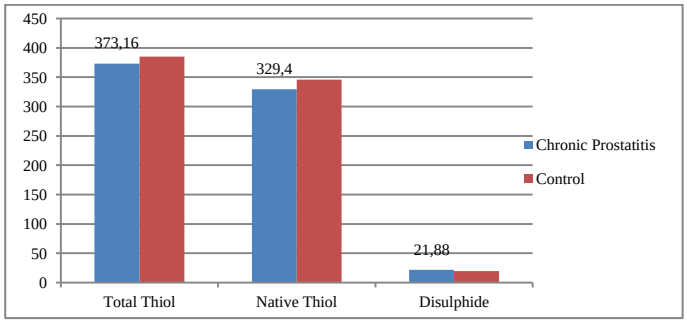
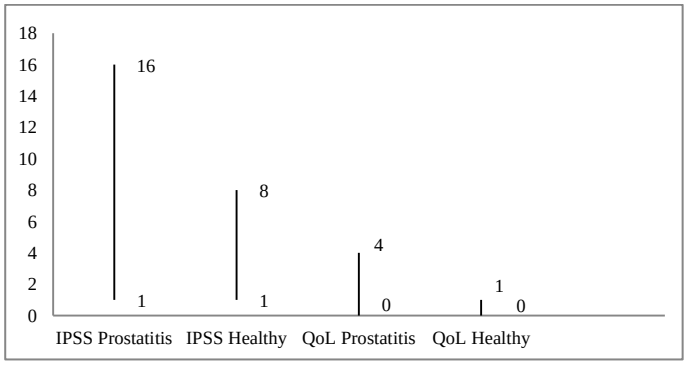


Figure 2: IPSS and QoL scores of the prostatitis and healthy groups



The SH, TT, SS, %SH/TT, %SS/SH, %SS/TT and PSA levels of the healthy volunteers were 45.61 (61.1) µmoL/L, 384.94 (67.76) µmoL/L, 19.66 (8.89) µmoL/L (Fig.1), 89.77 (4.17), 5.81 (2.57), 5.11 (2.08), and 1.07 (0.85) ng/ml, respectively. Their IPSS, QoL and Qmax were

4.05 (1.7), 1.4 (1.14) (Figure 2), and 17.11 (2.58) ml/sec, respectively. The chronic prostatitis patients and healthy controls significantly differed in terms of SH (P=0.043), SS/SH (P=0.037), IPSS (P=0.006), QoL (P=0.023), and Q_{max} (P=0.009) (Table 1). According to these results, the SH and Q_{max} values were significantly lower and the %SS/SH, IPSS and QoL values were significantly higher in the chronic prostatitis group compared to the control group.

Discussion

In urological practice, prostatitis a common condition seen more frequently among young and middle-aged men. It is estimated that around two million men admitted to hospital annually are diagnosed with prostatitis. However, true bacterial infections of the prostate constitute the minority of these cases [2]. In a study in which 409 men with prostatitis were retrospectively evaluated, bacterial cultures in prostate fluid were positive in only 10% [1]. This is due to the lack of parameters that would help in diagnosis. Maneuvers expressing the prostate fluid required for the diagnosis of chronic prostatitis are not practical, and thus rarely used in clinical practice. Clinicians need more practical biomarkers in the diagnosis and follow-up.

Prostatitis, the result of recurrent bacterial infections in chronic prostatitis, is classified as Category II. Diagnosis can be made by isolating bacteria in the prostatic fluid culture. However, the physiopathology of the chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) or Category III prostatitis is still not fully understood. Types of inflammatory (IIIA) or non-inflammatory (IIIB) prostatitis can be classified according to whether there are leukocytes in the prostate fluid. The available information on CP/CPPS is limited, and its etiopathogenesis is still poorly understood. For these reasons, the diagnosis and treatment criteria have not yet been precisely determined.

The causes of CP/CPPS include infection, autoimmunity, inflammation, and neurological conditions. Recently, the role of oxidative stress in CP/CPPS has also been investigated. Many studies show the role of oxidative stress in patients with chronic prostatitis, regardless of the etiological basis of CP/CPPS. Since inflammation in the tissue is always accompanied by oxidative stress in patients with chronic prostatitis, products of oxidative stress are seen in this condition [8]. In our study, we hypothesized that patients with chronic prostatitis would have more oxidative stress because we detected that the body reacted to destroy the radical products produced by stress, during which SH/SS homeostasis was impaired in favor of SS.

There are many publications regarding the relationship between inflammation and oxidative stress [8]. Different markers have been studied for ROS. In a healthy organism in which detoxifying and anti-inflammatory molecules effective against oxidative stress and inflammatory mediators are in balance, free radicals are at a normal level and necessary to a certain extent. Sometimes, while these free radicals cause damage, they can also promote repair [9]. Oxidative stress plays a key role in acute and chronic inflammation at various levels. There are many studies that reveal the effects of oxidative stress on chronic prostatitis, and oxidative stress markers have been identified in the urine and genital secretions of patients with prostatitis [10-13]. Studies have been conducted to explore the relationship between oxidative stress and prostate cancer, BPH and prostate inflammation [14]. Normal oxidative stress markers such as nitric oxide synthases and malonyl dialaldehyde are still in use today. However, the analysis technique found by Erel and Neselioglu is faster, cheaper, practical, and a fully automatic

spectrophotometric examination for the measurement of the plasma dynamic SH/SS homeostasis [5]. Dynamic SH/SS imbalance has been associated with various disorders, such as diabetes mellitus, cancer, migraine, hyperemesis gravidarum, obstructive sleep apnea, and chronic kidney failure [15].

Recently, the thiol metabolism has attracted attention as potential biomarkers of oxidative stress. Thiol protein groups are antioxidant buffers that regulate the redox system. Oxidative protein damage manifests itself with an increase in carbonyl levels and a decrease in thiol levels [16-18]. Decreased levels of thiol protein groups are associated with decreased serum antioxidant power. Therefore, SH/SS homeostasis can be considered an oxidative stress marker similar to lipid hydroperoxide, total antioxidant/oxidant status, and paraoxonase. Changes in SH/SS balance caused by oxidative stress provide valuable information concerning various abnormal biochemical processes [19]. It is known that thiol groups play a prominent role in ROS detoxification, and the reduction of thiol causes the failure of the antioxidant defense mechanism. SH/SS homeostasis and thiol oxidation have critical regulatory activities in oxidative stress, detoxification, regulation of enzymes, and protection against essential cellular pathways, such as signal transmission and pro-apoptotic and anti-apoptotic signaling [20]. If there is an increase in ROS in the environment, the organism uses thiol to destroy these harmful radicals, and as a result, the disulfide level increases. While oxidative stress products increase in inflammation, SH/SS homeostasis will be impaired in favor of SS. In their study comparing the BPH and control groups, Minciullo et al. [3] reported that the oxidative stress parameters were higher and antioxidant parameters were lower in prostate cancer [3]. This supports the shift of SH/SS homeostasis toward SS. Measuring this balance biochemically led us to consider that it could be an indicator of an inflammatory process associated with oxidative stress in tissue.

In a study on rats, the effects of oxidation on inflammation were demonstrated in subjects with chronic prostatitis. It was revealed that the use of antioxidants, such as diene conjugates, malonic dialdehyde, superoxide dismutase, and succinate dehydrogenase positively affected treatment in combating this inflammation [21], which indirectly supports our results. If the healing process is accelerated using antioxidants, this means that oxygen radicals accumulate in the tissue in cases of prostatitis. In our study, we found that the SH/SS homeostasis was impaired in favor of SS. This suggests that oxidative stress products are generated as a result of prostatitis. IPSS is a reproducible, validated index designed to determine disease severity and response to treatment. The use of IPSS alone is not safe in diagnosing BPH related lower urinary tract symptom (LUTS), but it is a quantitative measure of LUTS after diagnosis [22]. In LUTS, especially in BPH, IPSS is completed by patients. QoL is measured by adding further questions to IPSS.

Since chronic prostatitis causes LUTS, a significant difference was observed in the IPSS levels between the patients and healthy volunteer groups included in the study. In addition, the Q8 value, which was the QoL criterion based on urinary symptoms, was higher in the chronic prostatitis group than in the control group. Therefore, we consider that the use of IPSS and QoL forms in the follow-up of patients with chronic prostatitis will guide the evaluation of response to treatment.

The Q_{max} values of the patients with the complaints of LUTS were adversely affected. Bladder outlet obstruction can be safely diagnosed in men with a Qmax lower than 10 mL/s and an IPSS higher than 16 [23]. In a study conducted by Ghobish demonstrating the relationship between chronic prostatitis and voiding dysfunction, it was reported that Q_{max} value was decreased in patients with prostatitis compared to the control group [24].

We achieved similar results in our study. Q_{max} decreases not only in chronic prostatitis but also in bladder outlet obstruction or urethral stenosis. Thus, although Q_{max} alone is not sufficient for a diagnosis, we think it can aid in this process.

Chronic prostatitis negatively affects the quality of life. The procedures required for the diagnosis of chronic prostatitis in urology practice are not practical for the patient or the physician. Therefore, having a marker that can be used in diagnosis, treatment and follow-up may facilitate procedures to improve the patients' quality of life. Determining an impairment in SH/SS homeostasis through the method we used in the current study can assist clinicians in diagnosis. In addition, some studies have found that combating oxidative stress through anti-oxidants accelerates the improvement of the inflammatory process. We consider that positive changes in SH/SS homeostasis in the follow-up of the treatment can confirm the accuracy of the treatment during the inflammation process. It is also necessary to consider that diseases, such as oncological diseases, diabetes mellitus, and kidney disorders can also disrupt this balance.

Limitations

The main limitations of this study include the limited number of the study groups and the evaluation of changes in the level of SH/TT in other diseases, such as diabetes and cancer. Large-scale studies with a higher number of participants are needed.

Conclusions

We found that the SH level in patients with chronic prostatitis was low and their SS level was high; therefore, we think that the level of SH/TT may assist in supporting the diagnosis of chronic prostatitis. In addition, future studies investigating the role and efficacy of antioxidant treatment in chronic prostatitis can use this parameter to assess the effectiveness of treatment.

References

1. De la Rosette JJ, Hubregtse MR, Meuleman EJ, Stolk-Engelaar MV, Debruyne FM. Diagnosis and treatment of 409 patients with prostatitis syndromes. Urology. 1993;41:301-7.
2. Krieger JN, Nyberg L, Curtis Nickel JC. NIH Consensus Definition and Classification of Prostatitis. JAMA. 1999;282:236-7.
3. Minciullo PL, Inferrera A, Navarra M, Calapai G, Magno C, Gangemi S. Oxidative stress in benign prostatic hyperplasia: a systematic review. Urol Int. 2015;94:249–54.
4. Sies H. Oxidative stress: from basic research to clinical application. Am J Med. 1991;9:30-8.
5. Erel O, Neselioğlu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem. 2014;47:326-32.
6. Goodwin CJ. Research in psychology methods and design. Sixth ed. New Jersey: John Wiley&Sons, Inc: 2010. p.157-61.
7. Çapkın C. Statistical power analysis and it's use in nursing studies. Journal of Anatolia Nursing and Health Sciences. 2014:17:p271.
8. Ihsan AU, Khan FU, Khongorzul P. Role of oxidative stress in pathology of chronic prostatitis/chronic pelvic pain syndrome and male infertility and antioxidants function in ameliorating oxidative stress. Biomed Pharmacother. 2018 Oct;106:714-23.
9. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. Nature. 2000;408:239-47.
10. Paulis G. Inflammatory mechanisms and oxidative stress in prostatitis: the possible role of antioxidant therapy. Res Rep Urol. 2018;10:75–87.
11. Pasqualotto FF, Sharma RK, Potts JM, Nelson DR, Thomas AJ, Agarwal A. Seminal oxidative stress in patients with chronic prostatitis. Urology. 2000;55:881–5.

12.Shahed AR, Shoskes DA. Oxidative stress in prostatic fluid of patients with chronic pelvic pain syndrome: correlation with gram positive bacterial growth and treatment response. J Androl. 2000;21:669–75.
13.Kullisaar T, Türk S, Punab M, Mändar R. Oxidative stress – cause or consequence of male genital tract disorders? Prostate. 2012;72:977–83.
14.Solakhan M, Cicek H, Orhan N, Yildirim M. Role of native Thiol, total Thiol and dynamic Disulphide in diagnosis of patient with prostate cancer and prostatitis. Int Braz J Urol. 2019;45:495-502.
15.Topaktaş R, Ürkmez A, Kutluhan MA, Çalışkan S, Erel Ö. Does plasma thiol and disulphide be a new marker for prostate cancer in prostate-specific antigen level between 10 and 20 ng/ml? Aging Male. 2019 May 10:1-5.
16.Reznick AZ, Packer L. Oxidative damage to proteins: spectrophotometric method for carbonyl assay. Methods Enzymol. 1994;233:357–63.
17.Levine RL, Williams JA, Stadtman ER, Shacter E. Carbonyl assays for determination of oxidatively modified proteins. Methods Enzymol. 1994;233:347–57.
18.Hu ML. Measurement of protein thiol groups and glutathione in plasma. Methods Enzymol. 1994;233:380–5.
19.Sönmez MG, Kozanhan B, Deniz ÇD, Göger YE, Kilinç MT, Neşelioglu S, et al. Is oxidative stress measured by thiol/disulphide homeostasis status associated with prostate adeno carcinoma? Cent Eur J Immunol. 2018;43:174-9.
20.Hanikoglu F, Hanikoglu A, Kucuksayan E, Alisik M, Gocener AA, Erel O, et al. Dynamic thiol/disulphide homeostasis before and after radical prostatectomy in patients with prostate cancer. FreeRadicRes. 2016;50:S79-84.
21.Bratchikov OI, Dubonos PA, Tyuzikov IA. Justification of a Use of Additional Antioxidant Therapy in Experimental Models of Chronic Bacterial Prostatitis Urologiia. 2019;1:16-22.
22.D'Silva KA, Dahm P, Wong CL. Does this man with lower urinary tract symptoms have bladder outlet obstruction?: The Rational Clinical Examination: a systematic review. JAMA. 2014;312:535.
23.Porru D, Jallous H, Cavalli V, Sallustu F, Rovereto B. Prognostic value of a combination of IPSS, flow rate and residual urine volume compared to pressure-flow studies in the preoperative evaluation of symptomatic BPH. Eur Urol. 2002;41:246.
24.Ghobish A. Voiding Dysfunction Associated with "Chronic Bacterial Prostatitis". Eur Urol. 2002;42:159–62.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.