Research Results in Pharmacology

Research Results in Pharmacology 6(1): 11–19
UDC: 616.65–002.–615.272: 615.035.1
DOI 10.3897/rrpharmacology.6.50940

Research Article

Clinical and experimental rationale for antioxidant therapy of chronic bacterial prostatitis

Oleg I. Bratchikov[1], Igor A. Tyuzikov[2], Pavel A. Dubonos[1]

1 *Urology Department, Kursk State Medical University, 3 Karl Marx St., Kursk 305041, Russian Federation*
2 *Tandem-Plus Medical Center, 3V Pervomayskiy Lane, Yaroslavl 150000, Russian Federation*

Corresponding author: Oleg I. Bratchikov (bratov45@mail.ru)

Academic editor: T. Pokrovskaya ♦ **Received** 8 December 2019 ♦ **Accepted** 19 January 2020 ♦ **Published** 5 March 2020

Citation: Bratchikov OI, Tyuzikov IA, Dubonos PA (2020) Clinical and experimental rationale for antioxidant therapy of chronic bacterial prostatitis. Research Results in Pharmacology 6(1): 11–19. https://doi.org/10.3897/rrpharmacology.6.50940

Abstract

Introduction: Literature data prove the important role of oxidative stress in the pathogenesis of Chronic Bacterial Prostatitis (CBP) and its recurrence, which reduces the effectiveness of standard etiotropic therapy of the disease.

Aim of study: To improve the results of the pharmacotherapy of CBP by a comprehensive assessment of oxidative disorders in the prostate gland in a clinical and experimental study to provide evidence for antioxidant support.

Material and methods: The results of experimental simulation of CBP in 60 male rats and examination of 90 patients with CBP (average age 38.2 ± 1.4; main group) and 30 clinically healthy men (average age 35.5±1.5; control group), which included history-taking, collecting complaints, questioning, general and special examinations, biochemical, cytological, microbiological, sonographic studies. In some experimental animals and patients with CBP, different modes of pharmacotherapy were tested (antimicrobial monochemotherapy; antimicrobial chemotherapy+zinc picolinate; antimicrobial chemotherapy+L–carnitine tartrate in standard doses). The data were processed using descriptive and comparative statistics.

Results and discussion: Clinical and experimental findings showed the compensatory nature of the prostatic oxidative disorders after a standard antimicrobial monochemotherapy of the first episode of CBP and their continued persistence with a high risk of decompensation and development of mitochondrial dysfunction after a course of standard antimicrobial monochemotherapy in CBP recurrence. Zinc deficiency in the patients with CBP was detected on average 2.7 times more often than in the healthy men, so zinc determination in the prostatic fluid and subsequent drug compensation should be considered as first–line diagnostic and treatment measures. In the patients with CBP without zinc deficiency, L-carnitine may be an effective alternative to pharmacological correction of the prostatic oxidative disorders.

Conclusion: To increase the effectiveness of standard etiotropic therapy of CBP, simultaneous antioxidant support is necessary, using differentiated administration of antioxidants/antihypoxants (zinc or L-carnitine).

Keywords

Chronic bacterial prostatitis, experimental simulation, antimicrobial chemotherapy, free radical oxidation, lipid peroxidation, superoxide dismutase, succinate dehydrogenase, antioxidant, antihypoxant, zinc, L-carnitine.

Introduction

Chronic prostatitis (CP) is one of the most common urological diseases in men of different ages, but the results of its complex pharmacotherapy, even applying modern pharmacological achievements, in many cases can not be considered as satisfactory, which results, first of all, in a low quality of life of this category of patients (Nickel and Weidner 2000; Loran et al. 2002; Kogan et al. 2009; Belousov et al. 2013; Dosta and Sevostianov 2013).

One of the key reasons for this situation is the complex etiology and multi-factor nature of the CP pathogenesis, including its infectious (bacterial) type – chronic bacterial prostatitis (CBP), which makes up about 5–7% of the total structure of the disease types (Litwin et al. 1999; Engeler et al. 2018; Grabe et al. 2018).

Currently, it is understood that, in the etiopathogenesis and outcomes of CBP, an important role is played not only by direct negative effects of pathogenic microorganisms that cause direct reactions of alterations and inflammatory infection in the prostate tissue (inflammatory infection mechanisms), but also by a cascade of secondary non-infectious inflammatory biochemical reactions, which are induced by the infectious matter and inevitably involved in pathogenetic interaction with it and have adaptive and reparative nature (Kullisaar et al. 2012; Tyuzikov et al. 2013; Aoun et al. 2015; Molochkov et al. 2015). The level of prostate cells protection from the free radical oxidation arising as a result of inflammatory infection, as well as its further development and especially the outcomes determined by a degree of severity of structural damage and functional deficiencies in the prostate tissue after eradication of the pathogen from it and clinical and laboratory relief of CBP exacerbation depends on the safety, adequacy and direction of these secondary adaptive reactions (Tyuzikov et al. 2013; Grabe et al. 2018).

One of the key natural mechanisms of cellular adaptive reactivity is the antioxidant support network (ASN), consisting of various enzymatic and non-enzymatic natural antioxidants and present in all cells of the human body without exception (Kostyuk and Potapovich 2004; Mentschikova et al. 2006). An infectious agent in the prostate gland in CBP naturally leads to the primary activation of ASN in cells, which resists inflammatory infection and associated free radical oxidation, so a "biochemical scenario" of their development and outcomes largely depends on a degree of ASN compensation. In case of ASN failure or deficient, pathological processes in the prostate cells enhance and oxidative stress develops, often inducing additional anatomical and functional disorders in the organ (increased cellular alterations, violation of apoptosis in the cell, mitochondrial cell dysfunction, excessive peroxidation of cell membrane lipids, intracellular acidosis and hypoxia, etc.) (Kovalchuk et al. 2007; Kullisaar et al. 2012; Tyuzikov 2017).

In light of the above, it becomes evident that it is necessary to consider co-administration, along with antimicrobial chemotherapy, of pathogenetic medicines that support the activity of ASN in cell at the level sufficient to "kill" the excessive reactive oxygen species formed under oxidative stress on the background of inflammatory process, to optimize and improve the effectiveness of traditional etiotropic antimicrobial chemotherapy, which remains a first-line therapy in CBP. This would reduce the negative effects of inflammation and associated oxidative stress for prostate homeostasis and would be laying the groundwork for faster and more complete anatomical and functional recovery of the organ after eradication of the pathogen, since this problem is not solved by any of the antibiotics due to their lack of such a mode of action (Vicari et al. 2002; Balercia et al. 2017).

In modern urological practice, several pharmacological agents are used as effective antioxidants, of which zinc and selenium are the most studied. However, despite their popularity among urologists, zinc and selenium medications are often used in clinical practice without clear indications, without laboratory confirmation of the deficiency/insufficiency of these essential micro-elements, empirically and "blindly" (Cui et al. 2015; Sivkov et al. 2015; Mo et al. 2016). Such medicinal substance as L-carnitine, which is widely used in other fields of medicine and is a proven universal intracellular antioxidant with a known mechanism of action at the level of mitochondria of cells, which are the main cellular organelles that resist oxidative stress, is less studied in terms of its effectiveness as an antioxidant in the complex pharmacotherapy of CBP (Zhou et al. 2007; Ramasamy et al. 2012). The results of modern foreign studies show that due to the presence of high levels of oxidative stress in patients with CBP, L-carnitine administration in this disease can be explained from a pathogenetic point of view (Vicari et al. 2002; Condorelli et al. 2017; Shang et al. 2017). However, in the Russian scientific literature, the effectiveness of L-carnitine as an antioxidant in the treatment of CBP has been hardly studied, and L-carnitine medications available in Russia are used for a single indication – male infertility.

Currently, an active search for effective antioxidant drugs and rational modes of their administration in CBP is continuing (Balercia et al. 2017). However, according to the available Russian literature, a number of important practical issues of complex pharmacotherapy of CBP remain open, in particular, the sequence of applying etiotropic antibacterial and pathogenetic antioxidant therapies, the possibility of accurate laboratory diagnosis of deficiency/insufficiency of the most important natural antioxidants (for example, zinc) and the correlation of their plasma and prostatic concentrations, the definition of clear indications for the administration of the antioxidant depending on the clinical and laboratory features of CBP and a number of other treatment and diagnostic issues important for clinical practice.

Aim of study

Improving the results of the pharmacotherapy of Chronic Bacterial Prostatitis by a comprehensive assessment of the local oxidative disorders in the prostate gland in a

clinical and experimental study and to provide rationale for a differentiated combined etiopathogenetic pharmacotherapy with antioxidant support in this disease.

Material and methods

The study, which consisted of two parts – experimental and clinical, was organized and performed in accordance with the regulatory acts and guidelines governing the conduct of experimental and clinical research in the Russian Federation. Laboratory animals were treated in accordance with the current *Rules for the Use of Experimental Animals*, *International Guiding Principles for Biomedical Research Involving Animals* (1985) and Russian *Guidelines for Experimental (Pre-clinical) Studies of New Pharmacological Agents* (2000). All the patients who entered the main group of the clinical part of the study and completed it, as well as the men of the control group, had been previously informed of the aims and objectives of the study, and each of them filled in an informed consent for participation in the study and for using his personal results of the study for further statistical analysis.

The experimental part of study was performed in 60 outbred mature healthy male rats weighing 180–200 g, after a 14-day quarantine regime, without any signs of acute and chronic diseases. To simulate a laboratory model (CBP), a modified method by Nickel J. C.-Goto T. (1991) was used. The prostate gland and posterior urethra of male rats were infected by introducing a 0.05 ml and 0.1 ml of suspension of *E.coli NIHJ JC-2* culture at the concentration of 108 CFU/ml into the prostatic part of the urethra through a catheter. At the same time, 20 animals were infected once (experimental model of "CBP episode"), 20 animals were re-infected 30 days later (experimental model of "CBP recurrence"), and the remaining 20 intact animals made up the control group. After euthanasia, preparation and necessary studies of prostate homogenates of the laboratory animals were performed.

The clinical part was based on clinical observations, the results of complex examination and pharmacotherapy of 90 men (average age 38.2±1.4) with proven criteria for the diagnosis of chronic bacterial prostatitis, which were performed in the period of 2016–2018 in the outpatient departments of the Urology Clinic of Kursk State Medical University. The control group consisted of 30 clinically healthy men (average age 35.5±1.5) without prostate pathology. The total number of men included in the study was 120. The study was ongoing, prospective and full-design. The results of the complex examination of men in the control group were taken as normal reference values of the studied indicators.

Entry criteria:

- Presence of clinical CBP symptoms (the main clinical sign is chronic pelvic/prostatic pain with typical irradiation) in combination with appropriate laboratory validation (identification of significant pathogens in the prostatic fluid in a diagnostically significant titer $>10^3$ CFU/ml)
- Absence of a history of surgery or trauma of the pelvis and perineum
- No symptoms of any neurological disease
- No diabetes mellitus type 1 or type 2
- Absence of anamnesis and clinical and laboratory signs of infections (STIs) at the time of the study
- Age of men up to 50

Exclusion criteria:

- Presence of any clinical and sonographic signs of infravesical obstruction of any genesis
- Presence of lower urinary tract symptoms (LUTS) typical for overactive bladder
- Therapy of any LUTS or chronic pain earlier than 3 months ago, without any positive results
- Taking medications that can affect the bladder and/or prostate less than 6 months before the start of the study
- Known or suspected prostate cancer (total blood PSA > 4 ng/ml)
- Individual drug intolerance or contraindications to the medications used in this study.

Statistical processing of the age index of the control group (n = 30) showed an average age of 35.5 ± 1.5 years (confidence interval 0.95| 20–45), and for the patients of the main group (n = 90) the average age was 38.2 ± 1.4 years (confidence interval 0.95| 24–46). Thus, the control and main groups were homogeneous in age, since the confidence intervals overlapped in each group. The minimum duration of CBP was 1 year, the maximum duration was 13 years (the average duration of CBP was 7.5 ± 1.4 years; confidence interval 0.95| 1–13). The frequency and structure of the clinical symptoms of CBP in the main group are presented in Table 1.

Table 1. Frequency and Structure of the Clinical Symptoms of CBP in the Main Group (n = 90).

Clinical symptoms	Absolute number (people)	Percentage (%)
Pelvic/prostate pain syndrome with or without pain irradiation to adjacent anatomical regions	90	100.0
Increased anxiety and depression levels	38	42.2
Impaired productivity due to the chronic pain	36	40.0
Reduced sex drive	32	35.5
Reduced frequency and degree of morning and adequate erections	31	34.4
Orgasmic disorders	21	23.3
Inappropriate urination	15	16.7

Complaints and anamnestic data had been collected from all the men before the start of examination and treatment, in accordance with the generally accepted medical methods. To objectify and evaluate the severity of CBP and the quality of life of the patients after collecting anamnesis and complaints, a questionnaire was conducted using a valid questionnaire – NIH–CPSI–QL (National Institute of Health Chronic Prostatitis Symptom Index – Quality of Life). All men underwent general physical and special urological examination using standard methods. The laboratory examination of the prostatic fluid was performed using standard cytological and microbiological studies. To exclude concomitant sexually transmitted infections (STIs), urethral smears of all men in the main and control groups were examined using two methods: enzyme immunoassay (ELISA) and polymerase chain reaction (PCR). To determine the level of reactive oxygen species (ROS) in biological substances, the method of luminal-dependent chemiluminescence (LDCL) was used, based on the use of a mixture of a chemiluminescent probe – luminol (3-aminophthalhydrazide) – and horseradish peroxidase for accurate measurements of hydrogen peroxide formation. Determination of lipid peroxidation products (LPP) in biological substrates was performed using the following methods: diene conjugates were determined by the method of Stalnaya I.D. (1977); malondialdehyde was determined using spectrofluorometry after its reacting with thiobarbituric acid by the method of Stalnaya I.D. and Garishvili T.G. (1977). Superoxide dismutase (SOD) activity was determined by a spectrophotometric method, using the method of Mistra H.P., Fridovich I. (1972) modified by Kostyuk V.A. et al. (1990). Succinate dehydrogenase activity was determined by the method of Storozhuk P.G. and Storozhuk A.P. (2004), based on the ability of this enzyme to restore nitroblue tetrazolium (NBT) to formazan. In order to exclude prostate cancer, all the men of both groups at the initial stage of the study were determined the blood level of total PSA by a heterogeneous two-stage enzyme immunoassay, using standard Enzymun-Test PSA assays by BoehringerMannheim Corp. (Germany). The zinc content in the blood serum was determined by colorimetric method (IFCC), based on the formation of a colored complex compound of zinc with dithizone. The content of zinc in the prostatic fluid was determined by X-ray fluorescence analysis, based on the spectrum features of secondary fluorescence radiation of the sample, which occurs under the influence of harder X-rays. To test the reference parameters of the healthy men (prostate volume and its structure), as well as to assess the initial morphometric parameters of the prostate and their dynamics during observation and pharmacotherapy, all men of the main and control groups included in the study were subjected to transrectal US by a 5.5–7-MHz rectal biplane sensor (Ultramark-9, USA) and an ultrasound complex Logiq 500 Pro Series (USA). To assess the effectiveness of CBP treatment in the experimental and clinical parts of the study, several pharmacotherapy modes were tested (antimicrobial monochemotherapy (levofloxacin); antimicrobial chemotherapy + zinc picolinate; antimicrobial chemotherapy + L–carnitine tartrate in standard doses for 28 days). Statistical processing was performed in Microsoft Excel-2007 and Statistica 6.0. (StatSoft, USA). Data processing was performed using descriptive and comparative statistics. The results of the study were entered into a personal computer based on Microsoft Excel–2007 and Statistica 6.0. Spearman correlation coefficient (r) was determined to study the interaction among the quantitative features. The Student's t–test was used to evaluate the intergroup differences in the values of indicators that have a continuous distribution. To solve the problems of studying the influence of two or more conditions on a certain random variable, various statistical methods of multivariate analysis were used. The critical confidence level of the null statistical hypothesis (about the absence of significant intergroup differences or factor influences) was assumed to be 0.05. The value of $p<0.05$ generally accepted in biomedical research was considered as statistically significant for all indicators.

Results and discussion

In the experiment with simulated CBP episode, in the prostate tissue of the laboratory animals a significant increase in the processes of free radical oxidation was revealed (a significant 4.6-time increase in the number of ROSs, a 2-time increase in their activity, an increase in the level of intermediate lipid peroxidation products (diene conjugates and malondialdehyde) by 34.6% and 42.0%, respectively, a 1.5-time increase in the activity of superoxide dismutase (SOD) compared with those in the intact animals of the control group ($p < 0.05$), without significant dynamics of mitochondrial succinate dehydrogenase (SDH)). After the course of antimicrobial monochemotherapy, the number of ROSs in the prostate tissue was normalized, but their activity remained 1.6 time higher, the level of malondialdehyde was 20.1% higher and the activity of SOD – 19.7% higher, compared those of the control group ($p < 0.05$).

In the prostate gland of the laboratory animals with simulated CBP recurrence, significantly more pronounced cellular oxidative disorders were detected compared to the CBP episode model (a 7.6-time increase in the number of ROS, a 3.5-time increase in their activity, a 33.3% increase in SDH activity ($p < 0.05$) against the background of multidirectional changes in the level of lipid peroxidation products and a 32.0% lower SOD activity than in the control group ($p < 0.05$)). After a course of antimicrobial monochemotherapy, in the prostate tissue there remained significantly higher levels of ROS (3.45 times) and their activity (2.1 times) against a significantly lower (32.0%) level of SOD activity ($p < 0.05$) and unreliably lower (30.1%) level of mitochondrial SDH compared with those of the control group ($p < 0.1$).

The comparative clinical and laboratory characteristics of the control and main groups of the clinical part of the study are presented in Table 2.

Table 2. Clinical Characteristics and Indicators of the Oxidative Status in the Prostate Gland of the Men of the Control and Main Groups (n = 120).

Studying indicator (unit of measurement)	Control group (n=30) (mean value M ± m and confidential interval CI 0.95)	Main group (n = 90) (mean value M ± m and confidential interval CI 0.95)
Symptom severity assessment (points)	0.86 ± 0.2 (0–1)	8.5 ± 2.1* (5–17)
Overall symptoms score (points)	0.61 ± 0.1 (0–1)	12.2 ± 2.1* (9–27)
Pain index (points)	0.67 ± 0.2 (0–1)	4.9 ± 1.6* (6–14)
Life quality index (points)	0.62 ± 0.2 (0–1)	3.3 ± 0.8* (2–5)
Leucocytosis in the prostatic fluid (units/LPF)	6.5 ± 1.5 (0–10)	38.8 ± 10.2* (15–60)
Number of lecithin granules (units/LPF)	Moderate quantity in 27/30 (90.0%) Reduced quantity in 3/30 (10.0%)	Moderate quantity in 35/90 (38.9%)* Reduced quantity in 55/90 (61.1%)*
Prostatic Fluid Crystallization Test	Positive in 26/30 (86.7%)	Positive in 31/90 (34.4%)*
Light sum of the prostatic fluid (relative units)	1.35 ± 0.14 (1.11–1.78)	8.51 ± 0.35* (4.89–7.43)
Fluorescence peak amplitude of the prostatic fluid (relative units)	0.6 ± 0.1 (0.4–0.8)	2.1 ± 0.4* (0.9–2.8)
Diene conjugates in the prostatic fluid (nmol/ml)	8.2 ± 1.5 (4.5–10.1)	12.5 ± 1.2* (8.4–15.7)
Malondialdehyde in the prostatic fluid (nmol/ml)	0.56 ± 0.04 (0.50–0.62)	0.75 ± 0.03* (0.56–0.87)
SOD activity in the prostatic fluid (relative units/ml)	42.19 ± 2.14 (35.43–50.23)	78.34 ± 8.25* (63.56–92.55)

Note: *– statistically significant difference in comparison with the control group

As follows from Table 2, the differences in the clinical and laboratory indicators between the control and main groups were statistically significant ($p < 0.05$). In contrast to the healthy men of the control group, the patients with CBP had oxidative imbalance in the prostate gland (increased number and activity of ROS, increased leukocytosis of the prostatic fluid, and more lipid peroxidation and SOD activity in the prostatic fluid) and its secretory disorders (reduced number of lecithin granules in the prostatic fluid, the high frequency of the disorders of crystallization of the prostatic fluid), which, from the clinical point of view, corresponded to more pronounced symptoms of pain syndrome and more inferior quality of life in the patients with CBP compared with the healthy men in the control group ($p < 0.05$). In the patients with CBP, significant positive correlations were found between the amount of ROS and SOD activity in the prostatic fluid ($n = 90$; $r = 0.413$; $p = 0.001$) and between the amount of ROS in the prostatic fluid and the clinical pain index ($n = 90$; $r = 0.304$; $p = 0.001$).

The frequency of the absolute serum zinc deficiency in the patients with CBP was 28.9%, which is 2.89 times significantly higher than in the control group of healthy men (10.0%, respectively; $p < 0.05$). The frequency of the absolute zinc deficiency in the prostatic fluid in the patients with CBP was 41.1%, which is 2.5 times significantly higher than in healthy men of the control group (16.7%, respectively; $p < 0.05$). In general, the healthy men of the control group had a statistically significant weak positive correlation between the zinc levels in the serum and the prostatic fluid ($r = 0.156$; $n = 30$; $p = 0.001$), which turned out to be more statistically strong ($r=0.204$; $n=7$; $p = 0.001$) in the range of subnormal values (< 543 mcg/L) and the lower tercile of the reference normal values of serum zinc level (543–738 mcg/L). A statistically significant moderate positive correlation ($r = 0.345$; $n = 37$; $p = 0.001$) was also found in the patients with CBP with absolute zinc deficiency and lower limit of normal serum levels. The patients with CBP with zinc deficiency compared to the patients with CBP without it showed non-significantly worse clinical characteristics of pain and quality of life, non-significantly higher levels of leukocytosis, malondialdehyde and a lower content of lecithin granules in the prostatic fluid ($p < 0.1$), but significantly lower (by 20.2%) activity of SOD in the prostatic fluid ($p < 0.05$), between the activity of which and the concentration of zinc in the prostatic fluid a significant moderate positive connection was revealed ($r = 0.389$; $n = 90$; $p = 0.001$).

The integrative results of comparative evaluation of the effectiveness and tolerability of the CBP pharmacotherapy modes tested in this study are presented in Table 3.

As follows from Table 3, the standard antimicrobial monochemotherapy mode in contrast to the modes of combined pharmacotherapy with additional prescription of zinc and L-carnitine showed significantly worse results of microbiological eradication of pathogens and treatment in relation to the clinical characteristics of the disease, the quality of patients' life, secretory function of the prostate gland and especially its oxidative status ($p < 0.05$), which violations in the form of a hyperproduction of ROS and accumulation of the lipid peroxidation products (malondialdehyde) – along with a decreased SOD activity in the prostatic fluid continued to persist after a course of antimicrobial monochemotherapy.

Thus, the experimental findings showed the compensatory nature of oxidative changes in the prostate cells after standard antimicrobial monochemotherapy of the first episode of CBP (ASN compensation phase) and the continuing persistence of the oxidative disorders in the prostate cells after a course of standard antimicrobial monochemotherapy with a high risk of mitochondrial dysfunction in CBP recurrence (ASN decompensation phase).

The obtained results of the clinical part of the study also confirmed the negative impact of the infectious agent on the oxidative status of the prostate gland and reflected a significant role of free-radical prostatic aggression as an additional non-infectious component in the pathogenesis of pain syndrome in CBP.

Table 3. Integrative Comparative Evaluation of the Effectiveness and Tolerability of Various CBP Pharmacotherapy Modes (n = 75).

Studying indicator (unit of measurement)	Control group (n = 30) (average value M ± m and confidential interval CI 0.95)	Group 1 Etiotropic antimicrobial monochemotherapy (n = 15) (mean value M ± m and confidential interval CI 0.95)	Group 2 Combination therapy (antimicrobial chemotherapy + zinc picolinate) (n = 15) (mean value M ± m and confidential interval CI 0.95)	Group 3 Combination therapy (antimicrobial chemotherapy + L–carnitine tartrate) (n = 15) (mean value M ± m and confidential interval CI 0.95)
Microbiological efficiency (%)	–	86.7	93.3	100.0
Frequency of side effects (%)	–	20.1	6.7	6.7
Symptoms severity assessment (points)	0.86 ± 0.1 (0–1)	0.92 ± 0.3* (0–2)	0.76 ± 0.2 (0–1)	0.78 ± 0.3 (0–1)
Overall symptoms score (points)	0.61 ± 0.1 (0–1)	0.63 ± 0.3 (0–3)	0.62 ± 0.2 (0–2)	0.61 ± 0.3 (0–1)
Pain index (points)	0.67 ± 0.2 (0–1)	1.13 ± 0.2* (0–2)	0.71 ± 0.5 (0–1)	0.68 ± 0.3 (0–1)
Life quality index (points)	0.62 ± 0.2 (0–1)	0.98 ± 0.2* (1–3)	0.67 ± 0.4 (0–1)	0.63 ± 0.3 (0–1)
Leucocytosis in the prostatic fluid (units/LPF)	6.5 ± 1.5 (0–10)	11.5 ± 4.5 (8–14)	8.5 ± 2.5 (4–12)	6.5 ± 2.5 (0–10)
Number of lecithin granules (units/LPF)	Moderate quantity in 27/30 (90.0%) Reduced quantity in 3/30 (10.0%)	Moderate quantity in 6/15 (40.0%) Reduced quantity in 9/15 (60.0%)	Moderate quantity in 10/15 (66.7%) Reduced quantity in 5/15 (33.3%)	Moderate quantity in 9/15 (60.0%) Reduced quantity in 6/15 (40.0%)
Light sum of the prostatic fluid (relative units)	1.35 ± 0.14 (1.11–1.78)	2.06 ± 0.09*/** (1.61–2.83)	1.47 ± 0.05 (1.22–1.89)	1.37 ± 0.05 (1.15–1.81)
Fluorescence peak amplitude of the prostatic fluid (relative units)	0.6 ± 0.1 (0.4–0.8)	0.8 ± 0.2 (0.6–1.3)	0.7 ± 0.2 (0.5–1.1)	0.7 ± 0.1 (0.5–0.9)
Diene conjugates in the prostatic fluid (nmol/ml)	8.2 ± 1.5 (4.5–10.1)	8.1 ± 0.4 (6.4–10.5)	8.1 ± 0.2 (5.8–9.9)	7.8 ± 0.3 (5.2–9.1)
Malondialdehyde in the prostatic fluid (nmol/ml)	0.56 ± 0.04 (0.50–0.62)	0.68 ± 0.03*/** (0.72–0.90)	0.59 ± 0.03 (0.53–0.69)	0.58 ± 0.04 (0.51–0.70)
SOD activity in the prostatic fluid (relative units/ml)	42.19 ± 2.14 (35.43–50.23)	35.19 ± 2.87*/** (32.12–42.34)	40.76 ± 2.32 (37.12–48.54)	40.74 ± 2.17 (35.12–48.43)

Note: * – differences are statistically significant when comparing the indicators of the group treated by antimicrobial monochemotherapy with the indicators in the control group and both combination therapy groups ($p < 0.05$); ** –differences are statistically significant when comparing the indicators of the group treated by antimicrobial monochemotherapy and those of both combination therapy groups ($p < 0.05$)

Compared with the healthy men, the patients with CBP were on average 2.7 times more likely to have a deficiency of serum and/or prostatic zinc. Against the background of this, they had worse clinical and laboratory parameters of the disease and persisting oxidative disorders in the prostatic fluid in contrast to the patients with CBP without zinc deficiency. In routine clinical practice, direct zinc determination in the prostatic fluid should be considered as the most objective and informative method of zinc deficiency diagnosing in patients with CBP. Standard etiotropic antimicrobial chemotherapy of CBP does not guarantee a complete pharmacological cure of the prostate and has no affect on the course and outcomes of free-radical oxidation, which naturally develops against the background of the entry of an infectious agent into the prostate tissue. In this regard, additional prescription of medicinal agents that can safely and effectively neutralize the negative impact of oxidative stress on the prostate gland (antioxidants and/or antihypoxants) is pathogenetically substantiated to improve the results of modern CBP pharmacotherapy. Taking into account the crucial physiological role of zinc in prostate metabolism and the high frequency of zinc deficiency in patients with CBP, the first-line therapy in zinc-deficient patients with CBP is a medical correction of the deficiency of this essential micro-element. For patients with CBP without zinc deficiency, the administration of L–carnitine tartrate may be an effective and safe front-line therapy to correct the existing oxidative disorders in the prostate gland. The study showed a significant negative role of free-radical reactions in the formation of anatomical and functional disorders in the prostate gland in CBP, which are able to complete the "vicious loop" of its pathogenesis and maintain the organ alterations after a course of standard antimicrobial monochemotherapy (Fig. 1).

Based on the results of the study, the following practical algorithm for zinc deficiency diagnosing in patients with CBP is proposed (Fig. 2.).

An optimized algorithm for the sequence and differentiated administration of combined etiopathogenetic pharmacotherapy in CBP, based on the results of the study, can be presented as follows (Fig. 3).

The proposed practical algorithms are designed to improve the traditional diagnostic and pharmacotherapy of CBP carried out in a routine urological use and to implement an individual approach to the management of patients with this disease.

Conclusion

The obtained results of the clinical and experimental study convincingly confirmed the significant negative role of free radical oxidation (oxidative stress) induced by an infectious agent in the multifactorial pathogenesis of CBP, which has been reflected in the scientific literature of recent years. In this connection, it is possible to substantia-

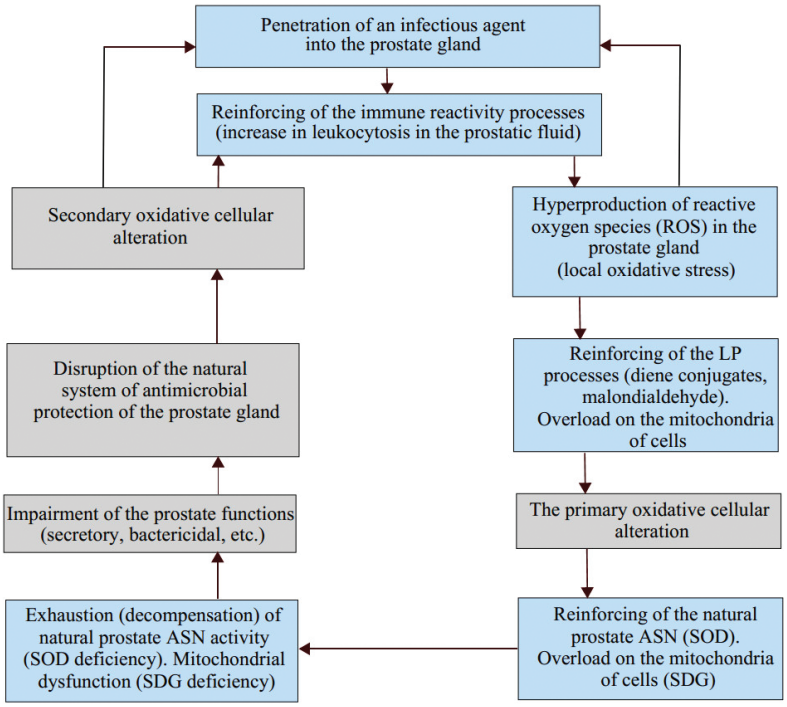

Figure 1. The role of oxidative local disorders in the prostate gland in the formation of the "vicious loop of pathogenesis" of CBP. Abbreviations: LP – lipid peroxidation; SOD – superoxide dismutase; SDG – succinate dehydrogenase; ASN – antioxidant support network.

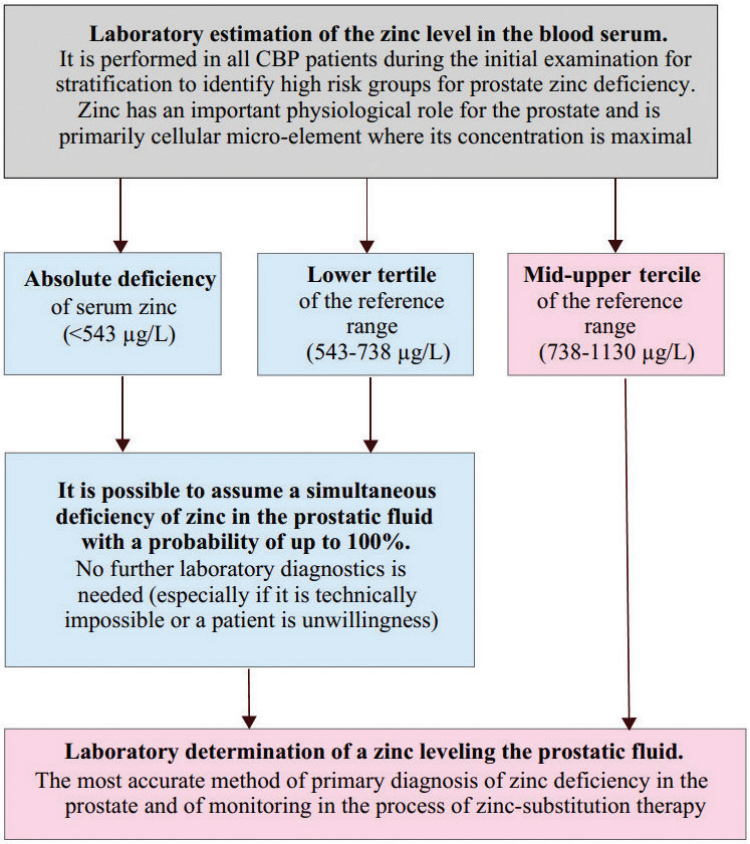

Figure 2. Diagnostic algorithm for zinc deficiency detecting in CBP patients in routine urological use.

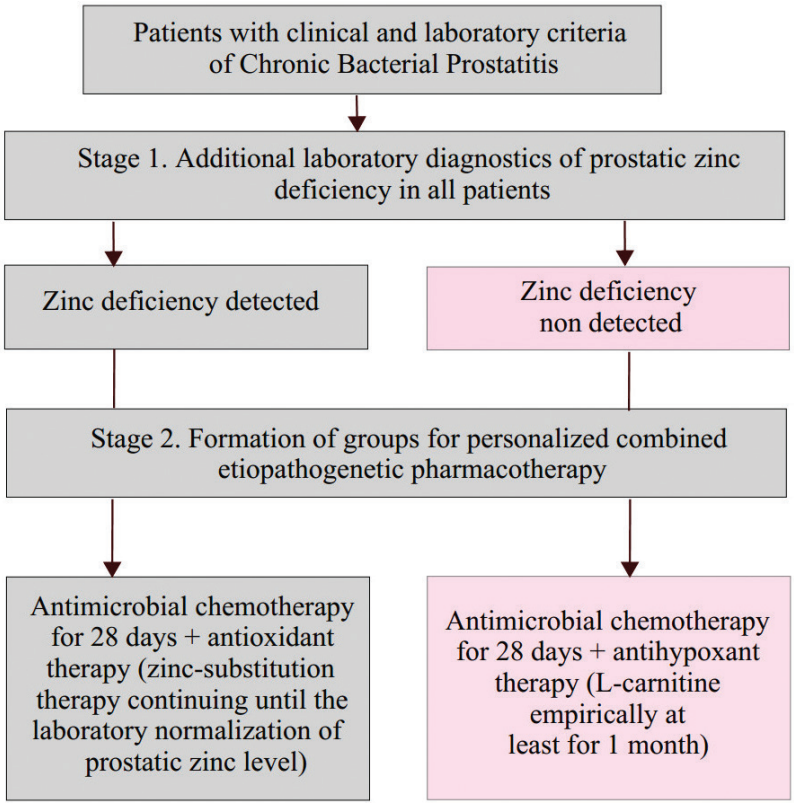

Figure 3. Algorithm of the sequence and differentiated choice of personalized combined etiopathogenetic pharmacotherapy in patients with CBP.

te with a high degree of confidence the need to optimize the existing methods of diagnostic and pharmacotherapy of this disease by personalized additional administration with etiotropic antimicrobial chemotherapy of medicinal agents with antioxidant/antihypoxant activity. At the same time, it should be noted that the practical side of the problem of pharmacological correction of oxidative cell disorders in CBP, namely, selecting specific drugs and their prescribing modes, as well as their effectiveness and tolerability in this type of the disease still remains understudied. In our opinion this is due to the obvious underestimation of the role of free–radical oxidation in this type of the disease by urologists (in clinical practice, when treating CBP, the main emphasis is placed solely on antimicrobial monochemotherapy), as well as to the fact that on the pharmaceutical market there is a large number of medicinal agents with claimed antioxidant/antihypoxant activity, many of which do not yet have sufficient evidence of a high degree of their efficiency in general and in CBP, in particular. As follows from the available foreign and Russian literature, various medicinal agents with the above-stated mechanism of action have been tested and continue to be tested as an antioxidant support for pharmacotherapy of chronic prostatitis.

As an effective and safe antioxidant support for standard antimicrobial chemotherapy of CBP, a targeted zinc replacement therapy (in zinc-deficient patients with CBP) and L-carnitine therapy (in all patients with CBP) can be recommended, which, according to the results of the clinical and experimental study described in the present paper, significantly increase the effectiveness of pharmacotherapy of this disease and are characterized by both good tolerance and compliance. It should also be noted that in the conditions of unsatisfactory results of standard antimicrobial chemotherapy of CBP, it quite promising to further search for, to study and to test new or already known medicinal agents with the ability to freely penetrate into the prostate tissue during the development of an inflammatory infection process in it and significantly reduce the severity of oxidative stress in it, since there are a few antioxidants/antihypoxants currently used in urology, and the effectiveness of the corresponding drugs is not always reliably proven.

Conflict of interest

The authors declare no conflict of interest.

References

- Aoun F, Marcelis Q, Roumeguère T (2015) Minimally invasive devices for treating lower urinary tract symptoms in benign prostate hyperplasia: Technology update. Research and Reports in Urology 7: 125–136. https://doi.org/10.2147/RRU.S55340 [PubMed]

- Balercia G, Gandini L, Lenzi A, Lombardo F (2017) Antioxidants in Andrology, Trends in Andrology and Sexual Medicine. Springer International Publishing, Switzerland. https://doi.org/10.1007/978-3-319-41749-3
- Belousov II, Chernogubova EA, Kogan MI (2013) The role of endothelial dysfunction in the pathogenesis of non-inflammatory form of chronic abacterial prostatitis. Urology [Urologiya] 3: 39–42. [in Russian]
- Condorelli RA, Russo GI, Calogero AE, Morgia G, La Vignera S (2017) Chronic prostatitis and its detrimental impact on sperm parameters: a systematic review and meta-analysis. Journal of Endocrinological Investigation 40(11): 1209–1218. https://doi.org/10.1007/s40618-017-0684-0 [PubMed]
- Cui D, Han G, Shang Y, Mu L, Long Q, Du Y (2015) The effect of chronic prostatitis on zinc concentration of prostatic fluid and seminal plasma: a systematic review and meta-analysis. Current Medical Research and Opinion 31(9): 1763–1769. https://doi.org/10.1185/03007995.2015.1072707 [PubMed]
- Dosta NI, Sevostianov NS (2013) Efficiency of application enzymotherapy in complex treatment of a chronic bacterial prostatitis. Medical News [Meditsinskie Novosti] 12: 72–76. [in Russian]
- Engeler D, Baranowski AP, Borovicka J (2018) Guidelines on Chronic Pelvic Pain. European Association of Urology, 90 pp. [in Russian]
- Grabe M, Bartoletti R, Bjerklund Johansen TE (2018) Guidelines on Urological Infections. European Association of Urology, 86 pp. [in Russian]
- Kogan MI, Belousov II, Shangichev AV (2009) Ischemic prostate disease as one of the causes of the urological syndrome of chronic pelvic pain. Consilium Medicum 11(7): 50–58. [in Russian]
- Kostyuk VA, Potapovich AI (2004) Bioradicals and bioantioxidants. Belorussian State University, Minsk, 174 pp. [in Russian]
- Kovalchuk LV, Gankovskaya LV, Mazo EB, Viryasov AV (2007) Analysis of cytokines in seminal plasma and serum of patients with chronic prostatitis during immunotherapy with a natural complex of cytokines and antimicrobial peptides. Journal of Microbiology Epidemiology Immunobiology 5: 57–61. [in Russian]
- Kullisaar T, Türk S, Punab M, Mändar R (2012) Oxidative stress-cause or consequence of male genital tract disorders? Prostate 72: 977–983. https://doi.org/10.1002/pros.21502 [PubMed]
- Litwin MS, McNaughton-Collins M, Fowler FJJr, Nickel JC, Calhoun EA, Pontari MA, Alexander RB, Farrar JT, O'Leary MP (1999) The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. Journal of Urology 162: 369–375. https://doi.org/10.1016/S0022-5347(05)68562-X [PubMed]
- Loran OB, Pushkar DYU, Segal AS, Yudovskiy SO (2002) Our understanding of the problem of chronic prostatitis. Pharmateca 10: 69–75. [in Russian]
- Mentschikova EB, Lankin VZ, Zenkov NK, Bondar IA, Krugovykh NF, Trufakin NA (2006) Oxidative stress -pro-oxidants and antioxidants. Slovo Corp., Moskow, 556 pp. [in Russian]
- Mo LJ, Chen X, Wang XM, Li GY, Zhang X, Huang S, Xie ZB, Mo ZN (2016) Reduced zinc concentration in expressed prostatic secretion relates to the pain symptoms of types and prostatitis. Zhonghua Nan Ke Xue [National Journal of Andrology] 22(6): 496–500. [PubMed]
- Molochkov VV, Ilin II, Molochkova YuV (2015) Chronic Urethrogenic Prostatitis. Maska Publishing House, Moscow, 302 pp. [in Russian]
- Nickel JC, Weidner W (2000) Chronic prostatitis current concepts and antimicrobial therapy. Infections in Urology 13(5): 22–28.
- Ramasamy R, Stahl PJ, Schlegel PN (2012) Medical therapy for spermatogenic failure. Asian Journal of Andrology 14(1): 57–60. https://doi.org/10.1038/aja.2011.63 [PubMed] [PMC]
- Shang Y, Liu C, Cui D, Han G, Yi S (2017) The effect of chronic bacterial prostatitis on semen quality in adult men: a meta-analysis of case-control studies. Scientific Reports 4: 7233. https://doi.org/10.1038/srep07233 [PubMed] [PMC]
- Sivkov AV, Romikh VV, Zakcharchenko AV (2015) Category IIIB chronic prostatitis/chronic pelvic pain syndrome and sexual dysfunction. Andrology and Genital Surgery [Andrologiya i Genital'naya Khirurgiya] 4: 18–26. [in Russian]
- Tyuzikov IA (2017) Oxidative stress as a key mechanism of aging: pathophysiological mechanisms and SMART diagnostics. Nutrition Issues [Voprosy Dietologii] 7(1): 47–54. https://doi.org/10.20953/2224-5448-2017-1-47-54 [in Russian]
- Tyuzikov IA, Grekov EA, Kalinichenko SYu, Martov AG (2013) Optimization of diagnostic of inflammatory diseases of the prostate on the basis of an interdisciplinary approach. Experimental and Clinical Urology [Eksperimentalnaya i Klinicheskaya Urologiya] 1: 44–51. [in Russian]
- Vicari E, La Vignera S, Calogero AE (2002) Antioxidant treatment with carnitines is effective in infertile patients with prostato-vesiculo-epididymitis and elevated seminal leukocyte concentration after treatment with non-steroidal anti-inflammatory compounds. Fertility and Sterility. 78(6): 1203–1208. https://doi.org/10.1016/S0015-0282(02)04350-9 [PubMed]
- Zhou X, Liu F, Zhai S (2007) Effect of L-carnitine and/or L-acetyl-carnitine in nutrition treatment for male infertility: a systematic review. Asia Pacific Journal of Clinical Nutrition 16 (Suppl. 1): 383–390. [PubMed]

Author contributions

- **Oleg I. Bratchikov**, Doctor of Medical Sciences, Professor, Head of the Department of Urology, e-mail: bratov45@mail.ru The author was engaed in research design, analysis of the obtained data, and the article-writing
- **Igor A. Tyuzikov**, Doctor of Medical Sciences, Professor, urologist, e-mail: phoenix-67@list.ru The author obtained the data for the analysis, analyzed the obtained data, and was engaged in the article writing.
- **Pavel A. Dubonos,** Postgraduate Student, Department of Urology, e-mail: v-utkin@rambler.ru The author reviewed the relevant literature and obtained the data for analysis.