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# Possible differential diagnosis of various chronic nonbacterial prostatites

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## Abstract

**Background:** The purpose of the study was to diagnose possible chronic nonbacterial prostatitis (CNP) and chronic pelvic pain syndrome (CPPS) among patients, as well as differentiate between the inflammatory (category IIIA) or non-inflammatory (category IIIB) types in selecting and optimizing differential drug treatment of this category of patients.
**Material and methods:** The study was conducted on 43 patients diagnosed with CNP/CPPS. The control group included 10 healthy men. Both the production of nitric oxides (NO) by phagocytes, as well as prostate secretion and ejaculate were determined according to the procedure described by Metelyskaya B.A., which was modified by Gudumac V, et al.
**Results**: There was a 39.0% ($p < 0.05$) decrease in NO production by induced NO-synthase (iNOS), determined in the blood of 11 patients (from the main group – 2) with CNP/CPPS and a 115% ($p < 0.05$) increase was determined in 32 patients (from the main group 1) if compared to the same indices in the control group. The prostatic secretion and ejaculate showed a higher macrophage iNOS activity by 80% ($p < 0.05$) and 75% ($p < 0.05$) if compared to the same parameters from the control group. The iNOS activity in prostatic fluid and split-ejaculate fractions from the main group – 2 did not differ from that of the control group.
**Conclusions:** The assessment of NO production, prostate secretion and ejaculate allows to somewhat establish the main diagnosis of CNP and category III types (A – inflammatory and B – non-inflammatory prostatitis), which will significantly contribute to the optimization and selection of an appropriate differential treatment based on the drug action mechanisms.
**Key words:** chronic nonbacterial prostatitis, nitric oxide, chronic painful pelvic syndrome, drugs.

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## Introduction

Chronic prostatitis is one of the most common and most difficult to diagnose andro-urological disease that is referred to polyetiological disorders. About 5-10% of chronic prostatitis cases prove to have a bacterial origin. The other 90-95% of cases are classified as "chronic nonbacterial prostatitis" unless the laboratory findings detect a bacterial cause (origin) [1]. Currently, it is also named as "chronic painful pelvic syndrome" [2].

According to the classification of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), chronic nonbacterial prostatitis / chronic pelvic pain syndrome (CNP/CPPS) is a category III prostatitis. The US National Institutes of Health classified and highlighted two types of chronic nonbacterial prostatitis / chronic pelvic pain syndrome (CNP/CPPS): inflammatory (IIIa) and non-inflammatory (IIIb) types [3].

The purpose of the study is to diagnose possible CNP/CPPS among patients, as well as differentiate between the inflammatory (category IIIA) or non-inflammatory (category IIIB) types in selecting and optimizing differential drug treatment of this category of patients.

## Material and methods

The study was carried on 53 men, of which 43 patients were diagnosed with CNP/CPPS, aged between 27 to 70 years (the mean age – 48.5 years), whereas the disease duration ranged from 5 to 14 years. The control group included 10 healthy men.

The diagnosis was established based on clinical data, anamnesis, digital rectal examination (DRE) and the Meares-Stamey four-glass test. In order to assess the symptoms of chronic prostatitis and its impact on patient quality of life, there were used the USA National Institutes of Health and the International Prostate Symptom Score (IPSS) systems, as well as the urine cytology, the urethral swab via the polymerase chain reaction, and the blood test on prostate-specific antigen; if required – urodynamic examination, cystoscopy, etc.

The serum nitric oxides (NO) content in phagocytic leukocytes, prostatic fluid and ejaculate were assayed by Griess reaction with diazotized sulphanilic acid (NO is a short-term molecule, which converts rapidly into nitrites, being determined via this reaction). The leukocyte suspension, separated from the blood, the prostate secretion

and ejaculate fraction were mixed with the substrate to obtain NO (to arginine) in saline solution, being incubated at 37°C over 24 hours; afterwards the Griess – Ilosvay (N-naphthylethylenediamine with sulphanilic acid) reagent was added to the studied sample. Over 15 minutes after pink discoloration, the photometry with a wavelength of 540 nm was performed according to the procedure described by Metelyskaya B.A., being modified by Gudumac V.S. et al. [4-6].

The data analysis was performed via statistical software SPSS-10 IBM Statistics for Windows, version 20 Microsoft Excel 2010, by using descriptive, variation, and correlational assessment methods. The quantitative parameters were determined by the mean value and the standard error value, whereas the t-Student criterion was used to estimate the statistical differences between the means of the two groups. The p-values below 0.05 (P <0.05) were considered statistically significant.

## Results and discussion

The assessment of the obtained results and the level of NO production by serum phagocytic leukocytes in prostate secretion and ejaculate showed that 32 patients with CNP/CPPS ( baseline group 1) had an increase of serum NO production by 115% (p <0.05), an increase of NO – macrophage synthase activity by 80% (p <0.05) in prostate secretion and by 75% (p <0.05) in ejaculate, compared to similar indices of patients from the control group (healthy men ) (tab. 1).

**Table 1. iNOS-induced NO production in blood, prostate secretion and spermoplasm of patients with chronic pelvic pain syndrome (M±m, n = 43 patients)**

| Study groups, n – patients | NO production | | |
|---|---|---|---|
| | Blood (μM/L) | Prostate secretion (μM/gram of protein) | Spermoplasm (μM/gram of protein) |
| Baseline group – 1 (n=32 patients) | 56.97 ± 0.94 ** | 7.58 ± 0.32 ** | 7.49 ± 0.42 ** |
| Baseline group – 2 (n=11 patients) | 16.1 ± 0.54* | 3.8 ± 0.82 | 3.9 ± 0.88 |
| Control group (n=10 healthy men) | 26.40 ± 0.25 | 4.21 ± 0.54 | 4.28 ± 1.2 |

Note: * – the value significance compared to the control group (p <0.05); ** – the significant value differences of the patients from the baseline study group (1 and 2) (p <0.05)

The iNOS-induced blood NO production decreased by 39.0% (p <0.05) in 11 patients (from baseline group-2) with CNP / CPPS, compared to the same parameter in the control study group (tab.1), whereas the iNOS activity in the prostate secretion and split ejaculate fraction for the same condition (CNP/CPPS) did not differ compared to the control group.

Therefore, a 3.5-fold increase (p <0.05) of NO production by NOS macrophage in the blood, in the prostate secretion and ejaculate in patients from the baseline group 1 (n = 32), compared to the 11 patients from the baseline group 2, shows the presence of an inflammatory response in the prostate of most patients with CNP / CPPS IIIA, and the non-inflammatory type of CNP/CPPS IIIB in 11 patients (from baseline group 2).

The assessment of the patients' overall condition determined the intensity of the pain syndrome in patients with CNP/CPPS IIIA (inflammatory CPPS type, n = 32) based on NIH-CPSI scale, which made up 10.84 ± 1.28 points, the urinary incontinence scored 9.64 ± 1,15 points, and the quality of life index was 11.00 ± 0.91 points. Patients with CPPS IIIB (non-inflammatory CPPS type, n = 11) had the following indices: 10.9 ± 1.1; 9.3 ± 1.0 and 10.9 ± 0.99, respectively. According to the IPSS scale, the urinary symptoms index was 13.44 ± 3.91 for CPPS IIIA (32 patients), and 14.1 ± 3.2 for IIIB (11 patients).

Based on the recent scientific research results [6-11], it has been established that chronic nonbacterial prostatitis refers to diseases that develop on the underlying disorders of proteolytic processes in the blood and prostate [8-13]. The mutual action of proteases and their inhibitors maintains the homeostasis within the body, whereas the successive complex and multi-component reactions are categorized as universal non-specific response to inflammation.

Shangichev A.V. et al. [11] stated that the disruption of the bioregulatory mechanisms of the body's main proteolytic systems, namely the kallikrein-kinin, is a major causative factor of CNP/CPPS [11]. The kallikrein-kinin system (SKK) plays a critical role in the pathophysiology of hyperalgesia and inflammatory diseases, as well as in the regulation of proteolytic cascade systems of blood plasma, kininogenesis, hemocoagulation, fibrinolysis, complement and renin-angiotensin system, which provide adaptation and protection of the body, particularly under stress condition. Kallikrein is a multifunctional proteinase that controls various biological processes, including converting the protein precursor kininogen into bradykinin that is a pain and inflammatory mediator [14-16]. Following a study analysis regarding the body's proteolotic systems that might induce an inflammatory response in the prostate, as well as on the markers of inflammation in blood and prostate secretion in various types of CNP/CPPS, Chernogubova I. A. [8] concluded that the inflammatory CNP / CPPS type, besides its subjective-objective inflammatory signs, such as pain and leukocytosis of prostate secretion, might be confirmed based on the status of proteolytic processes in prostate secretion, thus attesting an active inflammatory response in the prostate, being clinically manifested via the chronic pain syndrome. However, other particularities were found in patients with non-inflammatory types of CNP/CPPS. The lack of laboratory evidences of an active inflammatory response provides reason to assume that prostate inflammation initially "triggers" the pain syndrome occurrence, which although the inflammatory response subsides, the pain syndrome already persists due to some other mechanisms, including proteolytic activation of the blood. Thus, the non-inflammatory CNP/CPPS type, though clinically being a predominantly local

prostate disease, should be referred as a disorder associated with systemic pathogenetic mechanisms. According to the author, the metabolic pathways during an inflammatory response in chronic nonbacterial prostatitis are impaired due to the underlying imbalance in the proteinase-inhibitor system, uncontrolled proteolytic activity in the prostate and a weakened body's natural resistance, being the major causative factor of CNP/ CPPS.

Therefore, a significant interest to the pathogenesis and diagnosis of CNP/CPPS is shown to determining the superoxide dismutase activity (SOD) and catalase (CT) in the blood, prostatic secretion and ejaculate, as well as the NO production and its level in this category of patients, which might serve as biochemical markers in the development of an inflammatory response, being used to monitor the treatment effectiveness in patients with CNP/CPPS III.

The present research findings reported NO as a biochemical marker of inflammatory prostatitis in CNP / CPPS IIIA, by increasing the NO production in blood, in prostate secretion and ejaculate fraction. The high NO activity is likely to lead to the accumulation of superoxide and peroxynitrite in blood, prostatic secretion and ejaculate in case of CNP/CPPS IIIA. Excessive NO production in CNP/ CPPS is likely to increase the vessel wall permeability and thus leading to the impairment of the hematoprostatic and hematotesticular barrier gradient [17-19].

It is well known that the treatment of chronic prostatitis (CP) is an extremely challenging task. It depends on the patient's category and symptoms. Most patients present obstructive infravesical phenomena, sometimes being associated with irritative ones. There are several complex treatment approaches, which inevitably act on the etiology and pathogenesis of the disease. The use of new biologically active substances seem to offer great perspectives due to their complex immunostimulatory and antioxidant action. Recently, there have appeared a wide range of such drug classes (cytomedins and polypeptides, showing a systemic delivery and oriented effect (prostatotrope)). This treatment has its own peculiarities, depending on the patient's age and overall condition (immunity and mental status), presence and types of clinical manifestations, evolutionary peculiarities, stages of CP and the level of the adjacent organ involvement.

However, the obtained study results will contribute to an appropriate treatment selection, based on the drug action mechanisms and on the types of the underlying condition. Currently, these treatment schemes are subjected to considerable updating, including entomotherapy by using specific preparations (adenoprosine, imupurine, etc.) that exhibit anti-inflammatory, immunomodulatory and antioxidant properties [20-25].

## Conclusions

The NO production and its level in blood, prostatic secretion and ejaculate allows establishing the basic diagnosis of CNP , as well as determining category III (A- inflammatory and B- non-inflammatory types) prostatitis with its own characteristics, thus significantly optimizing the treatment due to an appropriate and differentiated selection of drugs depending on their action mechanism for patients with CNP/CPPS.

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**Author's contribution**
AC conceptualized the idea, conducted literature review, wrote the manuscript, revised and finalized the text.

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No competing interests were disclosed.