

Chronic bacterial prostatitis associated with androgen deficiency

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Abstract

Inflammation of the prostate gland occupies a significant proportion of inflammatory diseases of the genitourinary system. According to J. Potts et al. (2007), prostatitis is detected in 5–10% of the general male population. Today, one of the main problems associated with prostatitis is the narrowly targeted, often unwarranted treatment with its antibacterial drugs without taking into account the multifactorial nature of the pathogenesis and androgen dependence of the prostate gland. As a result, this leads to ineffective treatment of prostatitis amid growing antibiotic resistance. In turn, recent studies demonstrate key issues of testosterone and prostate gland relationship. These researches show that prostate metabolism is dependent on testosterone levels. The level of the hormone affects the course of chronic inflammation in the prostatic tissues. And also, that the number of bacterial agents that provoke pathological processes in the prostatic parenchyma directly depends on the degree of decrease in testosterone levels. This point of view is also supported by other studies. It was found that most patients with inflammation of the prostate gland had androgen deficiency, and correction of testosterone levels of these patients was highly effective in the treatment of chronic prostatitis. Thus, the androgen dependence of the prostate gland and the effect of hypogonadism on the incidence of prostatic parenchymal inflammatory changes allow us to radically revise the approach to the diagnosis and treatment of chronic bacterial prostatitis. The development and implementation of new algorithms in which the diagnosis and subsequent correction of concomitant androgenic are becoming a promising direction for this group of patients.

Keywords: chronic prostatitis, androgen deficiency, testosterone, antibiotic resistance, the effectiveness of the treatment of prostatitis.

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Chronic bacterial prostatitis (CBP) (type II, according to the classification of the US National Institute of Health 1995) is inflammation of the prostate gland (PG) that lasts more than three months. CBP is caused by bacteria and is accompanied by intermittent pain in the lower abdomen, perineal region, external genitalia, lumbosacral region, and/or impaired urination [1]. This is the most common urological disease in men under the age of 50 [2].

As far back as 1980, Stanford University Professor of urology T. Stamey considered chronic prostatitis (CP) to be “a wastebasket of clinical ignorance.” Unfortunately, this statement continues to remain relevant. In Russia, about 35% of men’s visits to a urologist are associated with CP [2]. Indeed, CP is a significantly common diagnosis in patients of outpatient urology in Russia and other countries. However, the results of standard pharmacotherapy remain unsatisfactory because of the as-

sociation with a high risk of clinical recurrence and progression of anatomical and functional disorders in the PG [3].

The problem of CP is multicausal, which in turn implies the need for a multidisciplinary approach to solving the problem of therapy of this pathology successfully. One of the main reasons is the poor-quality examinations of patients with CP. As a result, the prescription of ineffective therapy currently includes the non-optimal amount of standard diagnostic tests aimed only at identifying an infectious agent in the PG secretion. At the same time, most CBP pathogens are not revealed using standard nutrient media [3]. Also, many specialists do not consider the degree of prostatic homeostasis disorder, the key point of which is the androgen-dependence of the PG [4–7]. As a result, the approach to the treatment of CP is based largely on antibacterial therapy, which subsequently leads to

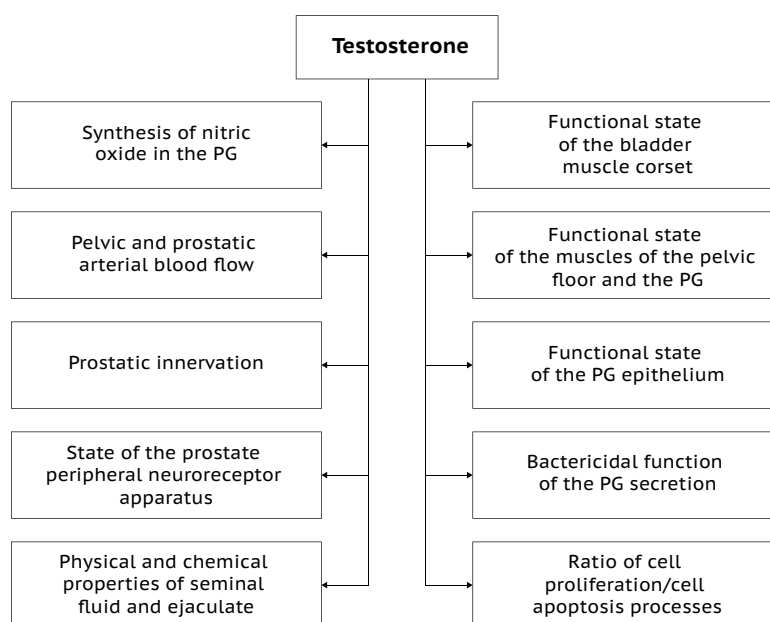


Fig. 1. The role of testosterone in prostate gland (PG) physiology. Adapted from [3].

a lack of effect from the treatment prescribed and a further increase in antibiotic resistance [3].

In matters of epidemiology, it is noteworthy that the bacterial nature of the disease is proven in no more than 10% of all cases of CP. In these cases, it is recommended to use the term “prostatitis” (acute or chronic) [8]. The remaining 90% of the disease in the presence of pain in the PG should be classified as “prostatic pain syndrome.” This is a constant or recurring pain syndrome in the PG region with a duration for at least three months during the last six months and has a non-infectious nature, unlike infectious prostatitis [8].

If the pain syndrome is not localized in the PG but is felt in the pelvic area, this condition should be classified as chronic pelvic pain syndrome, which requires diagnostic measures to clarify its etiology, since its causes may be pathological conditions that are not directly related to the genitourinary system [8]. Contemporary researchers explain such a low frequency of proven bacterial prostatitis with several points. The first point states that most methods of standard microbiological diagnostics of infection in the PG do not allow identification of anaerobic infection [3,9]. Also, inflammation in the PG tissues can often be caused by specific pathogens (chlamydia, mycoplasmas) that are related to intracellular bacteria, which can be detected only by polymerase chain reaction or special nutrient media [10]. Overweight individuals with a predominance of the visceral component of obesity, which is especially typical for patients with hy-

pogonadism, contributes to the implementation of cytokine mechanisms, which result in aseptic systemic inflammation, including in the PG tissues [11–13]. The above causes quite logically explain the increased number of leukocytes in the PG secretion with the use of sterile bacteriological cultures [11–13].

The PG is an immunocompetent organ, and in its metabolism, the “king of hormones,” testosterone (T), plays a decisive role. This is the main and most important circulating androgen, a steroid hormone that controls the development and preservation of male sexual characteristics. The central nervous system is directly responsible for the biosynthesis and secretion of T. Gonadotropin-releasing hormone is synthesized by the hypothalamus according to the negative feedback principle, which in turn affects the anterior lobe of the hypophysis. In response to this, the anterior lobe of the hypophysis secretes gonadolibrins, which are luteinizing and follicle-stimulating hormones that act on Leydig cells and Sertoli cells of the testicles [14]. Under the action of luteinizing hormone, more than 95% of T synthesis occurs in Leydig cells (the rest is produced by the adrenal glands), and spermatogenesis occurs in the Sertoli cells under the action of follicle-stimulating hormone [14].

T can have a direct effect on target cells that is mediated by an effect on androgen receptors, or it can be metabolized to 17β -estradiol by aromatase or to 5α -dihydrotestosterone by 5α -reductase [15]. The enzyme, 5α -reductase, is produced in signifi-

cant quantities in PG tissues and transforms T into 5α -dihydrotestosterone. Its biological activity exceeds T by 3–6 times, which is one of the main examples of the interaction of T and PG [16]. It should also be mentioned that aromatase, expressed mainly in adipose tissue, converts T to estradiol, which has an increased level in hypogonadism [17]. This observation provides a logical explanation for visceral obesity as one of the main risk factors for hypogonadism.

The multifaceted physiological functions of the PG and the role of T in their regulation should be considered and understood [3] (Fig. 1).

T serves as a regulator of the PG physiological functions, and the PG is one an essential link in the T synthesis regulation system [18]. A key role of T in PG metabolism is to ensure its bactericidal function [3]. Normally, an adequately functioning PG can protect itself independently from any infectious aggression, which is based on local and general mechanisms. These mechanisms include synthesis by the prostatic epithelium of zinc and citric acid ions, A and G immunoglobulins, spermine, lysozyme, and neutrophilic leukocytes, which normally are in a small amount almost always found within the prostatic secretion. This serves as the most important regulator of the PG bactericidal function, since several biologically active substances with pronounced immunomodulating effects are distinguished, among which is inducible nitric oxide (NO) synthase. Inducible NO synthase is a superactive oxidizing radical that exerts bactericidal influence on many microorganisms [19–22].

The bactericidal function, like all other physiological functions of the PG, is implemented in the process of natural metabolism and energy metabolism, which depend significantly on the level of androgenic saturation of the male body, which enables the use of some parameters of the PG secretion (in particular, the level of zinc and citric acid, a phenomenon of frond-like crystallization of secretion) as additional laboratory criteria for an adequate level of androgenic hormones [23].

Kogan et al. (2013) revealed that 37% of patients with CBP had T deficiency (total T < 12 nmol/L). In this study, patients with CBP were divided into three groups, which resulted in the demonstration of a very interesting relationship between the number of bacterial associations in the PG secretion and the blood level of total T. In patients in group 1 (T < 8 nmol/L) 4- and 5-component microbial associations prevailed (67.4%), and 3-component combinations of pathogens were recorded less often (32.6%). In group 2 (T = 8–12 nmol/L), 4-component and more associative relationships also prevailed (66%), and in

34% of cases, 3-component combinations of microorganisms were recorded. In group 3 (T > 12 nmol/L), 3-component associations were detected in 56.8% of patients. In 27.5% of cases, 2-component associations of pathogens were revealed, and 4-component variants were detected in only 15.7% of patients. As a result, we can conclude that the lower the T level in patients with CBP, the more diverse is the association of bacterial agents that provoked the PG inflammation [9].

Thus, a review of the modern literature revealed a new aspect that presented the PG as an androgen-dependent organ, as a result of which any disorders of synthesis and effects of T, in particular with hypogonadism, can be both a cause and a consequence of inflammatory changes in its tissues. In this regard, the development and implementation of diagnostic algorithms, as well as methods for the treatment of CBP associated with androgen deficiency, hold promise for this group of patients.

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REFERENCES

1. Alyaev Yu.G. *Bolezni predstatel'noy zhelezy*. (Prostate diseases.) Ed. By Alyaev Yu.G. M.: GEOTAR-Media. 2009; 107 p. (In Russ.)
2. Lopatkin N.A. *Natsional'noe rukovodstvo po urologii*. (Urology national guideline.) Ed. by Lopatkin N.A. M.: GEOTAR-Media. 2009; 538 p. (In Russ.)
3. Tyuzikov I.A., Kalinchenko S.Y., Vorslov V.O., Grekov Y.A. Correction of androgen deficiency in chronic infectious prostatitis as pathogenetic method of overcoming inefficiencies standard antibiotics against the growing antibiotic resistance. *Andrology and genital surgery*. 2013; (1): 55–63. (In Russ.) DOI: 10.17650/2070-9781-2013-1-55-63.
4. Tyuzikov I.A. The new pathogenic approaches to diagnostics of prostata diseases at men with obesity, androgen deficiency and diabetic neuropathy. *Andrology and genital surgery*. 2011; (4): 34–39. (In Russ.)
5. Tyuzikov I.A. Clinical and experimental parallels in pathogenesis of prostata diseases. *Sovr. probl. nauki obrazov.* 2012; (1): 57. (In Russ.)
6. Tyuzikov I.A., Martov A.G., Kalinchenko Y.S. Influence of obesity and androgen deficiency on prostatic blood circulation. *Bulletin of siberian medicine*. 2012; (2): 80–83. (In Russ.) DOI: 10.20538/1682-0363-2012-2-80-83.
7. Tyuzikov I.A., Martov A.G., Kalinchenko S.Y. New system mechanisms of pathogenesis of low urinary tract symptoms at men (literary review). *Bulletin of siberian medicine*. 2012; (2): 93–100. (In Russ.) DOI: 10.20538/1682-0363-2012-2-93-100.
8. Engeler D., Baranowsky A.P., Elneil S. et al. *Guideline on chronic pelvic pain syndrome*. European Association of Urology. 2012; 132 p.

9. Kogan M.I., Ibishev Kh.S., Chernyy A.A., Ferzauli A.Kh. Clinical characteristics of chronic bacterial prostatitis associated with testosterone deficiency. *Meditsinskiy vestnik Bashkortostana*. 2013; 8 (2): 91–94. (In Russ.)
10. Kogan M.I., Ibishev Kh.S., Chernyy A.A. *Defitsit testosterona u patsientov s khronicheskim bakterial'nyim prostatitom*. (Testosterone deficiency in patients with chronic bacterial prostatitis.) M. 2012; 32. (In Russ.)
11. Weinberg J.M. Lipotoxicity. *Kidney Int*. 2006; 70: 1560–1566. DOI: 10.1038/sj.ki.5001834.
12. Rohrmann S., De Marzo A.M., Smith E. Serum C-reactive protein concentration and lower urinary tract-symptoms in older men in the Third National Health and Nutrition Examination Survey (NHANES III). *Prostate*. 2005; 62: 27–33. DOI: 10.1002/pros.20110.
13. Lee M.J., Fried S.K. Integration of hormonal and nutrient signals that regulate leptin synthesis and secretion. *Am. J. Physiol. Endocrinol. Metab*. 2009; 296: 1230–1238. DOI: 10.1152/ajpendo.90927.2008.
14. Vierhapper H., Nowotny P., Waldhäusl W. Determination of testosterone production rates in men and women using stable isotope/dilution and mass spectrometry. *J. Clin. Endocrinol. Metab*. 1997; 82 (5): 1492–1496. DOI: 10.1210/jc.82.5.1492.
15. Molina P.E. Male reproductive system. In: H. Raff, M. Levitzky eds. *Medical physiology: A systems approach*. The McGraw-Hill Companies. 2011; 683–694.
16. Griffin J.E., Wilson J.D. Disorders of the testes and the male reproductive tract. In: P.R. Larson, H.M. Kronenberg, S. Melmed, K.S. Polonsky eds. *Williams textbook of endocrinology*. Philadelphia: W.B. Saunders. 2003; 709–769.
17. Weinbauer G., Luetjens C., Simoni M. et al. *Andrology*. Springer Berlin Heidelberg. 2010; 11–59. DOI: 10.1007/978-3-540-78355-8_2.
18. Arnol'di E.K. *Khronicheskiy prostatit: problema, opyt, perspektivy*. (Chronic prostatitis: problems, experience, prospects.) Rostov n/D: Feniks. 1999; 14 c. (In Russ.)
19. Lopatkin N.A. *Urologiya*. Natsional'noe rukovodstvo. (Urology. National Guideline.) Ed. by Lopatkin N.A. M.: GEOTAR-Media. 2009; 1024 p. (In Russ.)
20. Shcheplev P.A., Strachunskiy L.S., Rafal'skiy V.V. et al. *Prostatit*. (Prostatitis.) Ed. by Shcheplev P.A. M.: MED-Press-Inform. 2011; 224 p. (In Russ.)
21. Weidner W., Madsen P.O., Schiefer H.G. *Prostatitis: etiopathology, diagnosis and therapy*. NY: Springer. 1994; 276 p. DOI: 10.1007/978-3-642-78181-0.
22. World Health Organization, Department of Reproductive Health and Research. *WHO laboratory manual for the examination and processing of human semen*. Fifth edition. WHO. 2010; 287 p.
23. Kalinchenko S.Yu., Tyuzikov I.A. *Prakticheskaya andrologiya*. (Practical andrology.) M.: Prakticheskaya meditsina. 2009; 400 p. (In Russ.)