Chronic Prostatitis: Impact of Lifestyle, Infection, and Inflammation on Semen Parameters

Jennifer Puerta Suárez*, Valentina Velázquez Rivera†, Mateo Morales*, Angela M. Alvarez‡, Alejandro Carvajal†, Walter D. Cardona Maya*†

*Department of Microbiology and Parasitology, School of Medicine, University of Antioquia (UdeA), Medellín, Colombia; †Centre of Excellence in New Target Discovery (CENTD), Butantan Institute, São Paulo, Brazil; ‡Department of Urology, CES University, Medellín, Colombia

Abstract

BACKGROUND: Chronic prostatitis is a widespread disease of the prostate affecting men’s sexual and reproductive health worldwide. Its leading causes are urogenital tract infections by microorganisms with a prostate tropism.

AIM: This study aimed to evaluate semen parameters and the factors associated (lifestyle, urogenital infections, and inflammation) with the onset of chronic prostatitis symptoms.

MATERIALS AND METHODS: This case-control study included seventy-six donors: 30 volunteers with chronic prostatitis and 46 asymptomatic volunteers for urogenital infections as a control group. Sociodemographic, urinary symptoms, and lifestyle-related variables were collected in a survey. Seminal quality, cytokine levels in semen and serum, and the presence of nineteen microorganisms in the urogenital tract were evaluated.

RESULTS: Prostatitis was also associated with poor sperm morphology, more lipoperoxidation of the sperm membrane, and lower serum nitric oxide concentration. In addition, Neisseria gonorrhoeae infection was detected more frequently in semen samples from volunteers with chronic prostatitis. Volunteers with chronic prostatitis report more frequently erectile dysfunction and premature ejaculation, anxiety, depression, and stress compared to the control group.

CONCLUSIONS: Chronic prostate infections alter the microbiota from the genitourinary tract causing prostatitis, a disease that affects all life areas, including the familiar environment of patients. Chronic prostatitis affects seminal parameters, with a great impact on life quality and sexual and reproductive health. Despite being a relatively unexplored disease, much remains to be clarified regarding its diagnosis and treatment. Alterations in the genitourinary microbiota can favor sexually transmitted infections that produce chronic and systemic inflammation.

Introduction

Chronic bacterial prostatitis represents around 5–10% of cases in clinical practice. It is primarily caused by recurrent or antibiotic-resistant genitourinary tract infections (UTIs) that favor the chronicity of the infectious process, and it is also enhanced by the pathogen’s tropism for the prostate gland [1]. Although less frequently, viruses, protozoa, and fungi can also be responsible for certain cases of chronic prostatitis [2]. Non-bacterial infections in the prostate seem to play an essential role in male fertility, so their diagnosis, treatment, and prevention are necessary [2], [3], [4], [5], [6]. Microbiological detection techniques of causative agents are in large part based on bacterial cultures, and serology tests in cases of viral infections, especially those of sexual transmission. As in several chronic diseases, the association between lifestyle, sociodemographic variables, and many other factors with prostatitis symptoms has been investigated. Some factors have been described for chronic prostatitis, including urethral structure, urinary tract instrumentation, urethritis caused by sexually transmitted infections (STIs) [7], sedentary lifestyle, age, urinary retention, anxiety, smoking [8], and even periodontitis [9]. Chronic inflammation of the prostate is considered a risk factor as several inflammatory conditions may have a role in contributing to benign prostatic hyperplasia and prostate cancer development [10], [11]. In addition, chronic prostatitis can also affect male fertility; however, chronic prostatitis impact on male fertility is still controversial. Besides the known effects on quality of life [12], [13], prostatitis has a significant impact on individual’s mental health, as it increases levels of anxiety, depression, and stress, with negative effects on the patients’ family dynamics, social and workplace environment [3], [12]. Taking into account that chronic prostatitis is an apparently very common disease with failures in its diagnosis and treatment, which is associated with a strong impact on the quality of life of patients, the objective of this study evaluated the influence of lifestyle, urogenital
infections, and inflammation on semen quality in males with symptoms of chronic prostatitis.

Materials and Methods

Study participants

The study was approved by Bioethics Committee at the Institute of Medical Research, Medical School, University of Antioquia (Act number 006, April 26, 2018), and all donors gave their written informed consent. From May to October 2019, all men interested in participating in the study were included and subsequently classified as men with symptoms of chronic prostatitis or healthy controls.

This case-control study included seventy-six donors, thirty chronic prostatitis symptoms, and forty-six asymptomatic for urogenital infections volunteers based on the National Institute of Health of Chronic Prostatitis Symptoms Index [14] translated and validated into Spanish [15], according to the criteria reported by Nickel et al. [16]. In addition, all donors fulfilled a questionnaire containing personal data (sociodemographic factors, lifestyle, urinary symptoms, and other relevant aspects of sexual and reproductive health) that allowed us to identify factors associated with prostatitis symptoms.

Each donor gave a semen sample obtained by masturbation and a midstream urine sample. Both samples replaced the prostate fluid sample obtained through stimulation of the gland through the rectum [17]. A blood sample was taken by qualified personnel in a Vacutainer tube containing no anticoagulant (Becton Dickinson, NJ, USA) to obtain the serum.

Donors were excluded if they had UTI, epididymitis, prostatic surgery, genitourinary malignancy, pain from another source in the genitourinary tract, or reported any anti-inflammatory therapy.

Conventional seminal parameters

Semen samples were obtained by masturbation after a period of 2–5 days of sexual abstinence. The seminal parameters (volume, motility, viability, and sperm morphology) were evaluated following the World Health Organization criteria in the fifth edition of its Human Semen Processing Manual, while sperm concentration was evaluated using the Makler counting chamber [18], [19].

Functional seminal parameters

Functional parameters were evaluated by flow cytometry (Fortessa-Becton Dickinson, NJ, USA), analyzing 5000 and 10000 sperm cells. The cytometers were plotted and processed using the FlowJo 7.6 (Tree Star, Inc. OR, USA).

Sperm mitochondrial membrane potential

One million sperm were incubated with 0.25 mg/mL propidium iodide (PI, Molecular Probes® Inc, OR, USA) and 10 nm 3,3’dihexyloxacarbocyanine (DIOC6, Molecular Probes®) at 37°C for 30 min. It was centrifuged at 300 g for 5 min, and then the pellet was resuspended in 1X PBS (Gibco®, NY, USA) [20].

Sperm membrane integrity

One million sperm were incubated with 0.25 mg/mL of PI and 1 μM Sybr 14 (LIVE/DEAD® Sperm Viability Kit, Molecular Probes®) at 37°C for 30 min, and then was centrifuged at 300 g for 5 min and the pellet was resuspended in 1X PBS [21].

Chromatin structure assay

Five million sperm were resuspended in TNE buffer (TRIS-HCl, NaCl, EDTA - disodium, pH: 7.4), and just before reading the sample in the flow cytometer, 400 μL of acid detergent solution (HCl, NaCl, Triton X-100, pH: 1.2) and 30 s later the acridine orange dye solution (Sigma-Aldrich, MO, USA, 0.006mg/mL) were added [22].

Sperm membrane lipoperoxidation

One million spermatozoa were incubated with 5 μM 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY C11 Molecular Probes® Inc) at 37°C for 30 min, centrifuged at 300 g for 5 min, and then the sperm were resuspended in 1X PBS [23].

Intracellular levels of reactive oxygen species

One million spermatozoa were incubated with 1 μM 2’,7’dichlorofluorescein di-acetate (DCFH-DA, Sigma-Aldrich, MO, USA) and 0.25 mg/mL PI at 37°C for 5 min; 3 washes and centrifugations were carried out at 300 g for 5 min, and then the pellet was resuspended in 1X PBS [20].

Seminal plasma total antioxidant capacity

For this test, 3 mL of DPPH (2,2-diphenyl-1-picrylhydrazil) were mixed with 200 μL of the sample. After 1 h of incubation, the sample was read in a spectrophotometer at 515 nm, used ascorbic acid as a positive control [24].
Cytokine quantification in semen and serum samples by flow cytometry

Cytokines (IL-12p70, IL-10, IL-1β, IL-6, IL-8, TNF, IL-2, IL-4, IL-10, IL-17, and IFN-γ) were quantified in semen and serum samples using BD Cytometric Bead Array (CBA, Human Inflammatory Cytokines, and Human Th1/Th2/Th17 Cytokine Kit-Becton Dickinson, NJ, USA), following the manufacturer’s guidelines. All data were analyzed using FlowJo™ 7.6 Software (Becton Dickinson).

Prostate-specific antigen (PSA) quantification

Total PSA quantification in serum was performed using the commercial total PSA kit (DiaMetra, Perugia, Italy) according to the manufacturer’s instructions. Prostate antigen values >4 ng/mL were considered positive.

Nitric oxide

Nitrite quantification was performed using the commercial Griess Reagent Kit for Nitrite Determination (Molecular Probes® Inc) according to the manufacturer’s instructions and after deproteinization of the semen and serum samples according to the Serafini method [25].

Identification of microorganisms in semen samples by polymerase chain reaction

DNA extraction was performed using 500 μL of semen sample and the 10 mL urine pellet using the phenol-chloroform technique [26]. Briefly, the semen samples were centrifuged at 200 g for 10 min, and the urine samples were centrifuged at 22000 g for 10 min in aliquots of 2 mL with the subsequent mixing of the sediments. To each urine or semen sample, 0.5 mL of lysis solution (1M Tris, 0.5M EDTA, 5M NaCl, 10% SDS and 0.1% triton) and 5 μL of proteinase K were added for 12 h at 54°C. Subsequently, 1 mL of phenol-chloroform-isoamyl was added, and it was centrifuged at 5000 g for 10 min; 1 mL of absolute ethanol (−20°C), of 70% ethanol; the ethanol was allowed to dry, the precipitate the DNA. Finally, it was washed with 1 mL supernatant, and it was left at −20°C overnight to precipitate the DNA. Finally, it was washed with 1 mL of 70% ethanol; the ethanol was allowed to dry, the DNA was diluted in 100 μL of DNase/RNase-free water and quantified in a Nanodrop 2000 Spectrophotometer (Thermo Scientific, MA, USA).

The final 25 μL reaction volume contained 12.5 μL of Master Mix (Thermo-Scientific), a solution containing 0.025 U/L Taq DNA polymerase, 2 mM MgCl2, and 0.2 mM each dNTP (dATP, dCTP, dGTP, and dTTP); finally 0.2 μM of each primer, 2 μL of DNA (200 ng), and 9.3 μL of water were added to each reaction. The PCR was carried out in a T3000 thermal cycler (Whatman, Biometra, Goettingen, Germany), cycling conditions consisted of an initial denaturation step at 94–95°C for 5 min, followed by 35–40 cycles of specific conditions as previously, and a final elongation of 5–10 min at 72°C, using primers and following PCR conditions previously described [27]: β-actin [28], Chlamydia trachomatis [29], Escherichia coli [30], Klebsiella pneumoniae [31], Lactobacillus spp [32], Mycoplasma genitalium [29], Neisseria gonorrhoeae [29], Ochrobactrum atroby [33], Pseudomonas aeruginosa [31], Staphylococcus aureus [31], Staphylococcus epidermidis [34], Streptococcus agalactiae [35], Streptococcus pneumoniae [36], Streptococcus pyogenes [37], Treponema pallidum [29], Trichomonas vaginalis [29], Universal bacteria 27F y 1942R [38], Ureaplasma urealyticum [39], Herpes simplex virus I [29] and II [29], and Human papillomavirus [29].

DNA extracted from each bacterial strain or clinical isolates obtained from patients was used as a positive reaction control. Lactobacillus spp. DNA was obtained from a woman’s vaginal smear on day 14 of her menstrual cycle.

Statistical analysis

We performed descriptive statistics. A Chi-square and a Mann Whitney test were used to compare the dichotomous and numerical variables between the groups. The data were analyzed using the statistical program Graph Pad Prism 6.0 (GraphPad, CA, USA), and a value of p < 0.05 was considered significant.

Results

Lifestyle and its effect on chronic prostatitis

Both age (32 [range 21–50] years vs. 35 [range 18–50] years [p = 0.745]) and body mass index (25.5 kg/m² vs. 24.6 kg/m² [p = 0.195]) were similar between control group and the prostatitis symptoms group, respectively. Volunteers with prostatitis symptoms reported a higher frequency of previous urogenital tract disorders (8.7% vs. 30.0%, p = 0.0159) and consultations for infertility than the control group volunteers (0% vs. 10.0%, p = 0.0286) (Figure 1). The most frequently reported urinary symptom was urinary frequency (19.6% vs. 70.0%, p < 0.0001), and the most common anatomical site of pain was the perineum, followed by scrotum. Volunteers with prostatitis symptoms reported erectile dysfunction (2.2% vs. 26.7%, p = 0.0011) and premature ejaculation (4.4% vs. 33.3%, p = 0.0007) more frequently than control group volunteers (Figure 2). They also reported feeling anxiety (30.4% vs. 53.3%, p = 0.0459), depression (4.3% vs. 20.0%, p = 0.0298) and stress (19.6% vs. 26.7%, p = 0.0011) more frequently than control group volunteers. (Figure 3).
46.7%, \( p = 0.0119 \). Only 30% of the volunteers with prostatitis know their disease, and 10% have used antibiotics or anti-inflammatories. Additionally, 70% reported that their symptoms decrease with rest, and 33.3% reported that the symptoms interfere with their normal activities (Figure 3).

### Chronic prostatitis and seminal quality

Volunteers with chronic prostatitis symptoms have poor sperm morphology (5.8% vs. 4.4%, \( p = 0.0497 \)) and higher sperm membrane lipid peroxidation (45.8% vs. 70.8%, \( p = 0.0473 \)) (Table 1). In addition, volunteers with chronic prostatitis symptoms also present a lower concentration of nitrates in serum samples than men with prostatitis (3.16 \( \mu \)M vs. 2.16 \( \mu \)M, \( p = 0.0380 \)). The liquefaction time of the seminal samples was normal in both groups.

### STIs Frequency in chronic prostatitis

Chronic prostatitis symptoms volunteers have N. gonorrhoeae infection detected in urine samples (0% vs. 31.0%, \( p < 0.0001 \)) and in semen samples (0% vs. 24.1%, \( p = 0.0005 \)). Herpes simplex virus 1 infection was observed more frequently in urine samples in the control group (42% vs. 0%, \( p < 0.0001 \), although in semen samples, this result was not statistically significant (21.7% vs. 13.8%, \( p = 0.3898 \)). We did not detect the presence of herpes simplex 2, HPV, T. pallidum, and M. genitalium DNA in urine samples; these last two bacteria were also not detected in semen samples (Figure 4).

### Other microorganisms associated with chronic prostatitis

S. aureus DNA was detected more frequently in urine samples of chronic prostatitis symptoms.
volunteers (6.7% vs. 44.8%, p < 0.0001), but in that same sample, only S. pyogenes DNA was detected in control group volunteers (33.3% vs. 0%, p = 0.0005). Against the expectations, K. pneumoniae DNA was only detected in urine samples from control group (33.3% vs. 0%, p = 0.0005) (Figure 5). Lactobacillus spp. was detected more frequently in the semen samples from the control group (65.7% vs. 24.1, p = 0.0004). U. urealyticum, a controversial microorganism associated on some occasions with STIs and others with the microbiota, was detected more frequently in urine samples of control group volunteers (77.8% vs. 48.3%, p = 0.0088).

Table 1: Seminal quality in men with chronic prostatitis symptoms and asymptomatic men for urogenital infections

| Parameter                        | Control group | Chronic prostatitis group | p value |
|----------------------------------|---------------|---------------------------|---------|
| Volume (mL)                      | 2.75 (3.0–3.7) | 2.50 (0.8–11.8)           | 0.7481  |
| Progressive motility (%)         | 50.0 (3.0–81.0) | 50.0 (6.0–67.0)           | 0.9918  |
| Non progressive motility (%)     | 6.2 (0.0–50.0)  | 7.0 (1.0–25.0)            | 0.3684  |
| Concentration (sperm/mL)         | 84.5 (10.0–290) | 77.5 (0.0–220.0)          | 0.4561  |
| Viability (%)                    | 79.5 (36.0–92.0) | 82.0 (43.3–85.0)          | 0.4970  |
| Normal morphology (%)            | 9.0 (4.0–13.0)  | 4.4 (2.8–8.0)             | 0.0497  |
| Teratozoospermia index           | 1.26 (0.9–1.5)  | 1.26 (1.1–1.48)           | 0.8729  |
| High mitochondrial membrane potential (%) | 54.8 (12.9–73.5) | 51.7 (12.3–75.5)          | 0.6827  |
| Plasma membrane integrity (%)    | 60.7 (85.4–84.4) | 59.0 (12.1–79.6)          | 0.4848  |
| ROS production (%)               | 60.9 (21.7–86.2) | 53.8 (17.7–72.1)      | 0.3109  |
| DNA fragmentation index (%)      | 11.0 (10.1–14.9) | 11.9 (10.2–14.3)          | 0.7462  |
| Membrane lipid peroxidation (%)  | 45.8 (2.1–88.5)  | 70.8 (14.9–96.9)          | 0.0473  |
| Nitric oxide in serum (μM)       | 3.16 (0.07–17.1) | 2.16 (0.23–74.8)          | 0.0380  |
| Nitric oxide in plasma (μM)      | 0.95 (0.07–14.85) | 0.83 (0.07–9.91)          | 0.4824  |
| Prostate-specific antigen (ng/mL)| 0 (0–41.3)      | 0 (0–120.0)               | 0.1525  |

The role of inflammation in chronic prostatitis

Seminal plasma samples of men with chronic prostatitis symptoms presented an increased IL-2 concentration (10.35 pg/mL vs. 11.48 pg/mL, p = 0.0029). In serum samples, IL-2 also showed a higher concentration in volunteers with prostatitis (10.99 pg/mL vs. 12.02 pg/mL, p = 0.0067), as well as IL-6 (1.88 pg/mL vs. 25.68 pg/mL, p = 0.0120), and IL-17 (18.14 pg/mL vs. 19.31 pg/mL, p = 0.0344) (Figure 6).

Discussion

Chronic prostatitis is a disease of young adults under 50 years [8], [40], [41] characterized by voiding symptoms, genitourinary pain, and often sexual dysfunction, that may lead to impaired sexual and reproductive health [7], [8], [42], [43], [44], such as erectile dysfunction and premature ejaculation [42], [45], [46], [47], [48]. Erectile dysfunction is 3.6 times more common in men with chronic prostatitis symptoms [49], and up to 35% of patients with chronic prostatitis experience erectile dysfunction [48]. Premature ejaculation is one of the most common sexual dysfunctions, affecting up to 30% of men, with severe consequences on life quality such, leading to stress, frustration, and even desire to avoid sexual intercourse. In the present study, 26.7% and 33.3% of chronic prostatitis volunteers showed erectile dysfunction and premature ejaculation, respectively. Furthermore, Zhu et al., [45] reported that 26.8% of 1206 individuals with premature ejaculation have depression, and its psychological symptoms likewise impact their family, social, and work environment [12], [40], [48], [50]. Similarly, it has been described that more than 20% of patients with chronic prostatitis have depression [3].

The etiology of chronic prostatitis is not well-defined, albeit it has been proposed to define as an association of symptoms instead of a disease itself [40]. However, the inflammatory cardinal signs might not always be detected, especially in patients with chronic pelvic pain syndrome [51], where the autonomic nervous system plays an essential role in the genesis and maintenance of pain [13].

On the other hand, chronic prostatitis highly impacts life quality considering its frequency and complex treatment, which represents a notable economic, social, and emotional burden [3], [5], [6], [12], [13]. Besides, the factors associated with this disease have been widely studied, finding some controversial results. Lifestyles, diet, and practices related to sexual and reproductive health associated with chronic prostatitis, and its improvement may contribute to patients recovery [40]. Smoking and stress are also potential risk factors for developing chronic pelvic pain. Even so, smoking could, in a paradoxical way, improve pain sensitivity [8].

Regarding to erectile function, an erection occurs when endothelial nitric oxide synthesize and neuronal enzymes release, which increases the production of cyclic guanine monophosphate, favoring the relaxation of the arterial wall of the smooth muscle cells of the corpus cavernosum [49]. However, chronic prostatitis...
altered the relaxation of the arterial wall, and tadalafil has been proposed as a potential treatment [51]. In line with previous studies, we observed that volunteers had a decreased concentration of nitrites in serum compared to the control group (3.16 μM vs. 2.16 μM, p = 0.0380); this could explain why erectile dysfunction was more frequent in volunteers with chronic prostatitis symptoms.

Resistant chronic urinary infections are the leading cause of chronic prostatitis [52]. The infectious agents reach and colonize the prostate, and their elimination becomes problematic. New therapeutic measures such as the use of phytochemicals could lessen the impact of the disease [42]. Although UTIs are much less common in men than in women because of the length of the urethra, UTIs caused by Enterobacteriaceae can trigger prostatitis in men. In contrast to the traditional belief, the presence of microorganisms in the genitourinary tract does not imply disease; even the urinary tract can also harbor a microbiota [53]. In addition, there is a lack of prostatitis biomarkers and diagnostic methods [54], so little is known about this disease.

Among the STIs responsible for causing chronic prostatitis, infection with C. trachomatis and N. gonorrhoeae are most frequently reported. We detected N. gonorrhoeae infection in both semen and urine samples of volunteers with chronic prostatitis symptoms. This infection is the leading cause of urethritis in developing countries [55], which shows

Figure 4: Sexually Transmitted infections DNA detection

|                   | Urine          | Semen          |
|-------------------|----------------|----------------|
|                   | Control group  | Prostatitis    |
|                   |                |                |
| Micoplasma genitalium | >0.999         | >0.999         |
| Trichomonas vaginalis  | 0.3627         | 0.0616         |
| Herpes simplex virus 2 | >0.999         | 0.0710         |
| Herpes simplex virus 1 | <0.0001        | 0.3898         |
| Treponema pallidum  | >0.999         | >0.999         |
| Human papilloma virus | >0.999         | 0.7387         |
| Neisseria gonorrhoeae | <0.0001        | 0.0005         |
| Chlamydia trachomatis | 0.7078         | 0.1269         |

Chi-square

Figure 5: DNA detection of other bacteria associated with prostatitis

|                   | Urine          | Semen          |
|-------------------|----------------|----------------|
|                   | Control group  | Prostatitis    |
|                   |                |                |
| Ureaplasma urealyticum | 0.0088         | 0.4327         |
| Ochrobactrum anthropi | 0.0630         | 0.5940         |
| Lactobacillus spp.   | 0.4747         | 0.0004         |
| Staphylococcus aureus | <0.0001        | 0.9495         |
| Staphylococcus epidermidis | 0.4830        | 0.5652         |
| Streptococcus agalactiae | 0.1314        | 0.2048         |
| Streptococcus pneumoniae | >0.999       | 0.2048         |
| Streptococcus pyogenes | 0.0005         | 0.2486         |
| Pseudomonas aeruginosa | 0.2086         | 0.2486         |
| Klebsiella pneumoniae | 0.0005         | >0.999         |
| Escherichia coli    | 0.3627         | 0.6324         |

Chi-square
the role of STIs in the etiology of the disease [7]. In both semen and urine samples, C. trachomatis DNA was detected in both groups (urine: control 24.4% vs. prostatitis 20.7%, p = 0.7078; semen: control 10.9% vs. prostatitis 24.1%, p = 0.1279); although the effect on semen quality reported by Farahani et al. [56] was not observed. However, this agent was detected with high frequency when compared to that reported by Bielecki et al., [57], who observed a 10.8% prevalence of C. trachomatis in prostate biopsies from 65 volunteers aged 47–68 years who presented an increase in PSA or abnormal findings on palpation of the prostate in the andrological examination. T. vaginalis was detected more frequently in semen samples from volunteers with chronic prostatitis (4.3% vs. 17.2%, p = 0.0616); this microorganism has been associated with increasing risk of prostate cancer [10], [11]. Herpes simplex virus I was detected more frequently in urine and semen samples from the control group. However, this infection is widespread in the general population and does not have a substantial effect on male fertility [2]. Although human papillomavirus infection has been reported as a risk factor for developing chronic prostatitis [58], this association was not detected in the present study. K. pneumoniae DNA was detected more frequently in the urine samples of the control group volunteers; this microorganism has been considered microbiota across different anatomic sites, such as the skin and the gastrointestinal tract. However, on rare occasions, it has been identified in complicated infections such as prostate abscess [9].

Enterobacter is the most frequently reported genus in chronic prostatitis after STIs. The diagnosis of Enterobacteriaceae in chronic prostatitis depends on the methodology used, and E. coli is responsible for up to 80% of cases [17], [59]. Culture media for the growth of aerobic bacteria favors the detection of bacterial genus and limits the diagnosis of infectious agents that are difficult to culture. Even the diagnosis of chronic prostatitis is controversial when the cultures fail to detect enterobacteria [60]. Without discard the role of Gram-positive cocci in this disease [7], wherein the semen sample presents a high sensitivity for the diagnosis of both groups of microorganisms [61]. However, in men who experience symptoms of chronic prostatitis, only in 10% of prostatic fluid cultures is identified the bacteria [52]. In this study, the presence of 19 microorganisms was found, of which eight are responsible for STIs. In this subgroup, we omitted U. urealyticum despite being considered one of the microorganisms responsible for STIs that most commonly cause chronic prostatitis [7]. U. urealyticum is detected more frequently in infertile men and affects sperm concentration and morphology [56]; in addition, other researchers have considered this bacterium as a genitourinary microbiota acquired with the timing of first sexual intercourse [62]. In fact, in this study, the detection of DNA from this bacterium was more frequent in the urine and semen samples of the control group volunteers, but was only statistically significant in the urine sample.

Up to 10% of acute prostatitis cases end in chronic inflammation [7], and cytokine detection varies according to the time of the disease diagnosis. For instance, IL-17, crucial for the development of chronic pain, arises at the onset of the disease [63] and increases with alcohol intake [64]; this cytokine can even promote the transition from prostatitis to prostate cancer [65], [66]. As for IL-2 and IL-6, they were increased in serum samples in volunteers with prostatitis symptoms; IL-2 was also increased in seminal plasma, and both inflammatory cytokines may affect the seminal quality [67]. IL-6 is a cytokine of great importance in inflammation, and it is responsible for increasing the production of IL-2. Both IL-6 and IL-2 are increased in serum and seminal plasma of patients with chronic pelvic pain syndrome [4], [59], [68], [69]. In animal models of chronic pelvic pain syndrome, infiltrating macrophages and CD4 T cells can differentiate into subpopulations according to the microenvironment [11]. In general, Th1 and Th17 immune responses have been associated with the development of chronic pelvic pain [70]. Increased levels of TNF-α in prostatic fluid and semen has been considered a marker of inflammation in chronic pelvic pain syndrome and chronic prostatitis; it activates the NF-κβ pathway inducing the expression of inflammatory factors such as TNF-α itself, IL-1β and IL-6, promoting hyperalgesia [4]; however, no increase in this cytokine was observed in the participants of this study, as well as, we did not observe an increase in the cytokines IL-8, IL-10, IL-1β, and TNF-α, which were reported elevated in chronic prostatitis by other authors [59], [69], [71].

Our study had limitations. First, the filling out of the questionnaire of associated factors was done in the presence of researchers, who can make voluntaries increase or decrease the symptoms report based on the reliance with the investigators [45]. On the other
hand, the urethra is mainly colonized by Gram-positive cocci and Gram-negative bacilli that can contaminate the sample at the time of collection, so these results should be interpreted cautiously [61]. Second, the alterations in sexual function were self-reported by the volunteers, and yet, no validated questionnaire such as the International Index Erectile Function was applied [72]. Finally, the microbiological detection was carried out in semen and urine samples. Although the semen sample has high sensitivity and specificity for diagnosing infections, a negative result does not exclude the infection [17]. Despite these limitations, this is an excellent approximation to describe a common disease and its impact on life quality and sexual and reproductive health.

The results obtained through this research suggest that chronic prostatitis has multiple implications for male sexual and reproductive health. In the first place, it affects seminal quality by altering morphology and increasing sperm lipoperoxidation. Second, it is associated with STIs such as those caused by N. gonorrhoeae, and due to the obvious relationship of semen with sexual intercourse, these microorganisms can spread to the sexual partners of patients with prostatitis, increasing the prevalence of these infections. And finally, chronic prostatitis can affect male sexual function, increasing the prevalence of erectile dysfunction and premature ejaculation, which is also associated with increased stress and anxiety in men. Therefore, impacting the diagnosis and treatment of this disease can improve the quality of life of men.

Conclusion

Chronic prostatitis is associated with urogenital infections that cause chronic and systemic inflammatory processes and affect sexual health and life quality. STIs and especially N. gonorrhoeae infection is a risk factor for the development of chronic prostatitis. In addition, chronic prostatitis appears to be associated with erectile dysfunction, premature ejaculation, anxiety, depression, and stress. Although chronic prostatitis is frequent, men have a lack of knowledge about it. Men’s inclusion in public policies is necessary to improve their sexual and reproductive health.

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References

1. Puhr M, De Marzo A, Isaacs W, Lucia MS, Sfanos K, Yegnasubramanian S, et al. Inflammation, Microbiota, and Prostate Cancer. Eur Urol Focus. 2016;2(4):374-82. https://doi.org/10.1016/j.euf.2016.08.010
PMid:28723469

2. Gimenes F, Souza RP, Bento JC, Teixeira JJ, Maria-Engler SS, Bonini MG, et al. Male infertility: A public health issue caused by sexually transmitted pathogens. Nat Rev Urol. 2014;11(12):672-87.

3. Gaspar A, Silva J, Silva G, Anachelguez R, Prats J, Sagaz A, et al. Nonablative transurethral Erbium: YAG laser treatment for chronic prostatitis/chronic pelvic pain syndrome: A prospective comparative study. Neurourolog. 2020;40(1):278-85. https://doi.org/10.1002/nau.24551
PMid:33170523

4. Zhao Q, Yang F, Meng L, Chen D, Wang M, Lu X, et al. Lycopene attenuates chronic prostatitis/chronic pelvic pain syndrome by inhibiting oxidative stress and inflammation via the interaction of NF-kappaB, MAPKs, and Nrf2 signaling pathways in rats. Andrology. 2020;8(3):747-55. https://doi.org/10.1111/andr.12747
PMid:31880092

5. Nickel JC. Chronic prostatitis/chronic pelvic pain syndrome: It is time to change our management and research strategy. BJU Int. 2020;125(4):479-80. https://doi.org/10.1111/bju.15036
PMid:32250053

6. Motrich RD, Breser ML, Molina RI, Tissera A, Olmedo JJ, Rivero VE. Patients with chronic prostatitis/chronic pelvic pain syndrome show T helper type 1 (Th1) and Th17 self-reactive immune responses specific to prostate and seminal antigens and diminished semen quality. BJU Int. 2020;126(3):379-87. https://doi.org/10.1111/bju.15117
PMid:32437049

7. Videsnik Zorman J, Maticic M, Jeverica S, Smrkolj T. Diagnosis and treatment of bacterial prostatitis. Acta Dermatovenerol Alp Pannonica Adriat. 2015;24(2):25-9. https://doi.org/10.15570/actaapa.2015.8
PMid:26086164

8. Chen J, Zhang H, Niu D, Li H, Wei K, Zhang L, et al. The risk factors related to the severity of pain in patients with chronic prostatitis/chronic pelvic pain syndrome. BMC Urol. 2020;20(1):154. https://doi.org/10.1186/s12894-020-00729-9
PMid:33028277

9. Fu E, Cheng CM, Chung CH, Lee WC, Chen WL, Sun GH, et al. Association of chronic periodontitis with prostatic hyperplasia and prostatitis: A population-based cohort study in Taiwan. J Periodontol. 2021;92(1):72-86. https://doi.org/10.1002/jper.19-0706
PMid:32627845

10. Aglamis E, Ceylan C, Akin MM. Is there a correlation between the aggressiveness of chronic asymptomatic prostatitis National Institutes of Health category IV and the Gleason score in patients with prostate cancer? Can Urol Assoc J. 2020;14(11):E568-73. https://doi.org/10.5489/cuaj.6284
PMid:32520704

11. Liu Y, Mikrani R, Xie D, Wazir J, Shrestha S, Ullah R, et al. Chronic prostatitis/chronic pelvic pain syndrome and prostate cancer: Study of immune cells and cytokines. Fundam Clin Pharmacol. 2020;34(2):160-72. https://doi.org/10.1111/fcp.12517
PMid:31642541

12. Xu Y, Zhang L, Shen Y, Yao H, Yong S, You Y. Effectiveness
of psychological interventions for treating chronic prostatitis/chronic pelvic pain syndrome: A protocol for systematic review and meta-analysis. Medicine (Baltimore). 2020;99(39):e22151. https://doi.org/10.1097/MD.0000000000022151

PMid:32991409

13. Esfahli A, Farpour H, Hosseini A, Ahmed F, Chowdhury U, Nikbakht HA. Evaluation of the sympathetic skin response in men with chronic prostatitis: A case-control study. Res Rep Urol. 2020;12:239-45. https://doi.org/10.2147/RRU.S253101

PMid:32754453

14. Litwin MS, McNaughton-Collins M, Fowler FJ, Nickel JC, Calhoun EA, Pontari MA, et al. The National Institutes of Health chronic prostatitis symptom index: Development and validation of a new outcome measure. J Urol. 1999;162(2):369-75. https://doi.org/10.1016/s0022-5347(05)68562-x

PMid:10411041

15. Collins MM, O’leary MP, Calhoun EA, Pontari MA, Adler A, Eremenco S, et al. The spanish national institutes of health-chronic prostatitis symptom index: translation and linguistic validation. J Urol. 2001;166(5):1800-3.

PMid:11586227

16. Nickel JC, Downey J, Hunter D, Clark J. Prevalence of prostatitis-like symptoms in a population based study using the national institutes of health chronic prostatitis symptom index. J Urol. 2001;165(5):842-5.

PMid:11176483

17. Montes LZ, Mejia AA, Munarriz CA, Gutierrez EC. Semen and urine culture in the diagnosis of chronic bacterial prostatitis. Int Braz J Urol. 2008;34(1):30-7; discussion 8-40. https://doi.org/10.1590/s1677-55382008000100006

PMid:18341719

18. World Health Organization. WHO Laboratory Manual for the Examination and Processing of Human Semen. Geneva: World Health Organization; 2010.

19. Cardona-Mayawa W, Berdugo J, Cadavid A. Comparing the sperm concentration determined by the makler and the neubauer chambers. Actas Urol Esp. 2008;32(4):443-5.

PMid:19540481

20. Mayorga-Torres B, Cardona-Mayawa W, Cadavid A, Camargo M. Evaluation of sperm functional parameters in normozoospermic fertile individuals. Actas Urol Esp. 2013;37(4):221-7. https://doi.org/10.1016/j.acuro.2012.06.008

PMid:23246107

21. Martinez-Pastor F, Mata-Campuzano M, Alvarez-Rodriguez M, Alvarez M, Anel L, de Paz P. Probes and techniques for sperm evaluation by flow cytometry. Reprod Domest Anim. 2010;45(Suppl 2):67-78. https://doi.org/10.1111/j.1439-0531.2010.01622.x

22. Evenson DP, Larson KL, Jost LK. Sperm chromatin structure assay: Its clinical use for detecting sperm DNA fragmentation in male infertility and comparisons with other techniques. J Androl. 2002;23(1):25-43. https://doi.org/10.1002/j.1399-4602.2002.tb02599.x

PMid:11780920

23. Attken RJ, Wingate JK, De Iuliis GN, McLaughlin EA. Analysis of lipid peroxidation in human spermatozoa using BODIPY C11. Mol Human Reprod. 2007;13(4):203-11. https://doi.org/10.1093/molehr/gal119

PMid:17327268

24. Gil-Villa AM, Cardona-Mayawa W, Agarwal A, Sharma R, Cadavid A. Assessment of sperm factors possibly involved in early recurrent pregnancy loss. Fertil Steril. 2010;94(4):1465-72. https://doi.org/10.1016/j.fertnstert.2009.05.042

PMid:19540481

25. Serafini M, Maiani G, Ferro-Luzzi A. Alcohol-free red wine enhances plasma antioxidant capacity in humans. J Nutr. 1998;128(6):1003-7. https://doi.org/10.1093/jn/128.6.1003

PMid:9614160

26. Suárez JP, Maya WD. Prevalence of Chlamydia trachomatis, Neisseria gonorrhoeae and Ureaplasma urealyticum in semen samples: Effects on sperm quality. Urol Colombiana. 2016;25(3):219-24.

27. Rivera VV, Maya WD, Suárez JP. The relationship between sexually transmitted bacteria, microbiota and seminal quality in asymptomatic men. Asian J Urol. 2021. https://doi.org/10.1016/j.ajur.2021.09.004

28. Schmittgen TD, Zakrjaske A, Mills AG, Gom V, Singer MJ, Reed MW. Quantitative reverse transcription-polymerase chain reaction to study mRNA decay: Comparison of endpoint and real-time methods. Anal Biochem. 2000;285(2):194-204. https://doi.org/10.1006/abio.2000.4753

PMid:11017702

29. Gimenes F, Medina FS, de Abreu AL, Irie MM, Esquicati IB, Malagutti N, et al. Sensitive simultaneous detection of seven sexually transmitted agents in semen by multiplex-PCR and of HPV by single PCR. PLoS One. 2014;9(6):e98862. https://doi.org/10.1371/journal.pone.0098862

PMid:24921247

30. Lee C, Kim J, Shin SG, Hwang S. Absolute and relative QPCR quantification of plasmid copy number in Escherichia coli. J Biotechnol. 2006;123(3):273-80. https://doi.org/10.1016/j.jbiotec.2005.11.014

PMid:16388869

31. Anbazhagan D, Mui WS, Mansor M, Yan GO, Yusof MY, Sekaran SD. Development of conventional and real-time multiplex PCR assays for the detection of nosocomial pathogens. Braz J Microbiol. 2011;42(2):448-58. https://doi.org/10.1590/S1517-8382201001000006

PMid:24031653

32. Fu C, Carter J, Li Y, Porter J, Kerley M. Comparison of agar plate and real-time PCR on enumeration of Lactobacillus, Clostridium perfringens and total anaerobic bacteria in dog faeces. Lett Appl Microbiol. 2006;42(5):490-4. https://doi.org/10.1111/j.1477-765X.2006.01893.x

PMid:16652008

33. Kulikarni G, Gohil K, Misra V, Kakrania AKR, Misra SP, Patel M, et al. Multilocus sequence typing of Ochrobactrum spp. isolated from gastric niche. J Infect Public Health. 2017;10(2):201-10. https://doi.org/10.1016/j.jiph.2016.04.013

PMid:27287730

34. Vandeesteele S, Peetersmans W, Merckx R, Van Eldere J. Quantification of expression of Staphylococcus epidermidis housekeeping genes with Tagman quantitative PCR during in vitro growth and under different conditions. J Bacteriol. 2001;183(24):7094-101. https://doi.org/10.1128/JB.183.24.7094-7101.2001

PMid:11717267

35. Kong F, Ma L, Gilbert GL. Simultaneous detection and serotype identification of Streptococcus agalactiae using multiplex PCR and reverse line blot hybridization. J Med Microbiol. 2005;54(12):1133-8. https://doi.org/10.1099/jmm.0.46244-0

PMid:16278425

36. Kais M, Spindler C, Kalin M, Ortvist Å, Giske CG. Quantitative detection of Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis in lower respiratory tract samples by real-time PCR. Diag Microbiol Infect Dis. 2006;55(3):169-78.

PMid:16626914

37. Zhao X, He X, Li H, Zhao J, Huang S, Liu W, et al. Detection of Streptococcus pyogenes using rapid visual molecular assay. FEBS Microbiol Lett. 2015;362(18):fnv148. https://doi.org/10.1093/med/2010.4753

PMid:15177026
38. Frank JA, Reich CI, Sharma S, Weisbaum JS, Wilson BA, Olsen GJ. Critical evaluation of two primers commonly used for amplification of bacterial 16S rRNA genes. Appl Environ Microbiol. 2008;74(8):2461-70. https://doi.org/10.1128/AEM.02272-07

PMid:18296538

39. Tapia JR, Torres MC, Olea MS, Preval NR. Prevalencia de ureaplasma urealyticum en mujeres. Rev Mex Patol Clin. 2004;51(1):33-6.

40. Zhang J, Liang C, Shang X, Li H. Chronic prostatitis/chronic pelvic pain syndrome: A disease or symptom? Current perspectives on diagnosis, treatment, and prognosis. Am J Mens Health. 2020;14(1):1557988320903200.

41. CoSkun A, Can U, Tarhan F, Kavukoğlu O, Narter KF. The preliminary results of a Mediterranean survey. Arch Ital Urol Androl. 2020;92(4):353. https://doi.org/10.4081/aiau.2020.4.353

PMid:33297296

42. Zhang K, Guo RQ, Chen SW, Chen B, Xue XB, Chen S, et al. The efficacy and safety of Serenoa repens extract for the treatment of patients with chronic prostatitis/chronic pelvic pain syndrome: A randomized, double-blind, placebo-controlled trial. World J Urol. 2021;39(9):3489-95. https://doi.org/10.1007/s00345-020-03577-2

PMid:33452912

43. Stamatiou K, Magri V, Perletti G, Samara E, Christopoulos G, Trinchieri A. How urologists deal with chronic prostatitis? The preliminary results of a Mediterranean survey. Arch Ital Urol Androl. 2020;92(4):353. https://doi.org/10.4081/aiau.2020.4.353

PMid:33348966

44. Li G, Chang D, Chen D, Zhang P, You Y, Huang X, et al. Efficacy of radial extracorporeal shock wave therapy for chronic prostatitis/chronic pelvic pain syndrome: A protocol for systematic review. Medicine (Baltimore). 2020;99(44):e22981. https://doi.org/10.1097/MD.0000000000022981

PMid:33126371

45. Zhu O, Dou X, Tang L, Tang D, Liao G, Fang W, et al. Prevalence of prostatitis-like symptoms and outcomes of NIH-CPSI in participants with lifelong and acquired PE: Based on a large cross-sectional study in China. Biomed Res Int. 2017;2017:3473796.

46. Li HJ, Kang DY. Prevalence of sexual dysfunction in men with chronic prostatitis/chronic pelvic pain syndrome: A meta-analysis. World J Urol. 2016;34(7):1009-17. https://doi.org/10.1007/s00345-015-1720-3

PMid:26546073

47. Birowo P, Rangganata E, Rasyid N, Atmoko W. Efficacy of radical extracorporeal shockwave therapy for the treatment of chronic non-bacterial prostatitis: A systematic review and meta-analysis. PLoS One. 2020;15(12):e0244295. https://doi.org/10.1371/journal.pone.0244295

PMid:33370372

48. Li XC, Zhang XB, Liao ZC, TangZY, Li DJ. Is mild erectile dysfunction associated with severe psychological symptoms in Chinese patients with moderate-to-severe chronic prostatitis/chronic pelvic pain syndrome? Asian J Androl. 2021;23(3):319-24. https://doi.org/10.4103/aja.aja_71_20

PMid:33208565

49. Wang GC, Huang TR, Hu YY, Wang KY, Shi H, Yin L, et al. Corpus cavernosum smooth muscle cell dysfunction and phenotype transformation are related to erectile dysfunction in prostatitis rats with chronic prostatitis/chronic pelvic pain syndrome. J Inflamm (Lond). 2020;17:2. https://doi.org/10.1186/s12950-019-0233-z

PMid:31911760

50. Cui X, Naveed M, Baig M, Wang W, Mikrani R, Liu Z, et al. Therapeutic effects of Qianlie Tongli decoction on chronic prostatitis/chronic pelvic pain syndrome induced by peptide T2 in mice. J Pharm Pharmacol. 2020;72(10):1434-46. https://doi.org/10.1111/jpp.13525

PMid:32648958

51. Hiramatu S, Tsujimura A, Soejima M, Yoshiyama Y, Ishikawa K, et al. Taladafil is sufficiently effective for severe chronic prostatitis/chronic pelvic pain syndrome in patients with benign prostatic hyperplasia. Int J Urol. 2020;27(1):53-7. https://doi.org/10.1111/iju.14122

PMid:31587411

52. Su ZT, Zenilman JM, Sfanos KS, Herati AS. Management of chronic bacterial prostatitis. Curr Urol Rep. 2020;21(7):29. https://doi.org/10.1007/s11934-020-00978-z

PMid:32488742

53. Aragon IM, Herrera-Imbroda B, Queipo-Ortuno MI, Castillo E, Del Moral JS, Gomez-Millan J, et al. The urinary tract microbiome in health and disease. Uro Eur Focus. 2018;4(1):128-38. https://doi.org/10.1016/j.euf.2016.11.001

PMid:28753805

54. Suskind AM, Berry SH, Ewing BA, Elliott MN, Suttorp MJ, Clemens JQ. The prevalence and overlap of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome in men: Results of the RAND interstitial cystitis epidemiology male study. J Urol. 2013;189(1):141-5. https://doi.org/10.1016/j.juro.2012.08.088

PMid:23164386

55. Horner PJ, Martin DH. Mycoplasma genitalium infection in men. J Infect Dis. 2017;216(Suppl 2):S396-405.

56. Farahani L, Tharakan T, Yap T, Ramsay J, Jayasena C, Minhas S. The semen microbiome and its impact on sperm function and male fertility: A systematic review and meta-analysis. Andrology. 2021;9(1):115-144. https://doi.org/10.10111/andr.12886

PMid:32794312

57. Bielecki R, Ostaszewska-Puchalska I, Zdrodowska-Stefanow B, Baltaziak M, Skawronska M, Sokolowska M. The presence of Chlamydia trachomatis infection in men with chronic prostatitis. Cent Eur J Urol. 2020;73(3):362-8. https://doi.org/10.5173/cejuro.2020.0040

PMid:33133666

58. Jain P, Ghosh A, Jana D, Pal DK. Chronic pelvic pain syndrome/chronic prostatitis: Is it related to human papillomavirus infection? A case-control study from Eastern India. Urologia. 2020;87(3):137-41. https://doi.org/10.1111/andr.12886

PMid:31942833

59. Ho DR, Chang PJ, Lin WY, Huang YC, Lin JH, Huang KT, et al. The urinary tract microbiome in patients with chronic prostatitis/chronic pelvic pain syndrome. J Inflamm (Lond). 2020;17:2. https://doi.org/10.1186/s12950-019-0233-z

PMid:31911760

60. Tanner MA, Shoskes D, Shahed A, Pace NR. Prevalence of corynebacterial 16S rRNA sequences in patients with bacterial and “nonbacterial” prostatitis. J Clin Microbiol. 1999;37(6):1863-70. https://doi.org/10.1128/JCM.37.6.1863-1870.1999

PMid:10325338
Scand J Urol Nephrol. 2006;40(4):326-31. https://doi.org/10.1080/00365590600748247
PMid:16916775
62. Holmes K, Stamm W, Piot P, Wasserheit J, Corey L, Cohen M. Sexually Transmitted Diseases. 4th ed. New York: McGraw Hill; 2008.
63. Murphy SF, Schaeffer AJ, Done J, Wong L, Bell-Cohn A, Roman K, et al. IL17 mediates pelvic pain in experimental autoimmune prostatitis (EAP). PLoS One. 2015;10(6):e0125623. https://doi.org/10.1371/journal.pone.0125623
PMid:25933188
64. Zhang LG, Chen J, Meng JL, Zhang Y, Liu Y, Zhan CS, et al. Effect of alcohol on chronic pelvic pain and prostatic inflammation in a mouse model of experimental autoimmune prostatitis. Prostate. 2019;79(12):1439-49. https://doi.org/10.1002/pros.23866
PMid:31233226
65. Zhang Q, Liu S, Parajuli KR, Zhang W, Zhang K, Mo Z, et al. Interleukin-17 promotes prostate cancer via MMP7-induced epithelial-to-mesenchymal transition. Oncogene. 2017;36(5):687-99. https://doi.org/10.1038/onc.2016.240
PMid:27375020
66. You Z, Guo N, Shen G, Zhang Y, Moustafa AA, Ge D. Interleukin-17 promotes migration and invasion of human cancer cells through upregulation of MTA1 expression. Front Oncol. 2019;9:546. https://doi.org/10.3389/fonc.2019.00546
PMid:31281798
67. Castiglione R, Saleni M, Vicari LO, Vicari E. Relationship of semen hyperviscosity with IL-6, TNF-alpha, IL-10 and ROS production in seminal plasma of infertile patients with prostatitis and prostatic-vesiculitis. Andrologia. 2014;46(10):1148-55. https://doi.org/10.1111/and.12207
PMid:24329571
68. Liang W, Wu Z, Zhang G, Chen W, Hu X, Yang J, et al. A urine-based biomarker for chronic prostatitis/chronic pelvic pain syndrome: A retrospective multi-center study. Transl Androl Urol. 2020;9(5):2218-26. https://doi.org/10.21037/tau-20-1268
PMid:33209686
69. Peng X, Guo H, Chen J, Wang J, Huang J. The effect of pirfenidone on rat chronic prostatitis/chronic pelvic pain syndrome and its mechanisms. Prostate. 2020;80(12):917-25. https://doi.org/10.1002/pros.23995
PMid:32569423
70. Zhang M, Liu Y, Chen J, Chen L, Meng J, Yang C, et al. Single-cell multi-omics analysis presents the landscape of peripheral blood T-cell subsets in human chronic prostatitis/chronic pelvic pain syndrome. J Cell Mol Med. 2020;24(23):14099-109. https://doi.org/10.1111/jcmm.16021
PMid:33124198
71. Liu J, Yu J, Peng X. Poria cocos polysaccharides alleviates chronic nonbacterial prostatitis by preventing oxidative stress, regulating hormone production, modifying gut microbiota, and remodeling the DNA methylome. J Agric Food Chem. 2020;68(45):12661-70.
72. Hao ZY, Li HJ, Wang ZP, Xing JP, Hu WL, Zhang TF, et al. The prevalence of erectile dysfunction and its relation to chronic prostatitis in Chinese men. J Androl. 2011;32(5):496-501. https://doi.org/10.2164/jandrol.110.012138
PMid:21233394