



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

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Abstract

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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, pain location, sexual and reproductive health, 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 cytometries 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'-dihexyloxycarbocyanine (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 300g 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-1 β , 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 μ L 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 μ L 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), 50 μ L of 3M sodium acetate was added to the recovered 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 μ L of DNase/RNase-free water and quantified in a Nanodrop 2000 Spectrophotometer (Thermo Scientific, MA, USA).

The final 25 μ L reaction volume contained 12.5 μ L 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 μ M of each primer, 2 μ L of DNA (200 ng), and 9.3 μ L 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 atrophy* [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.

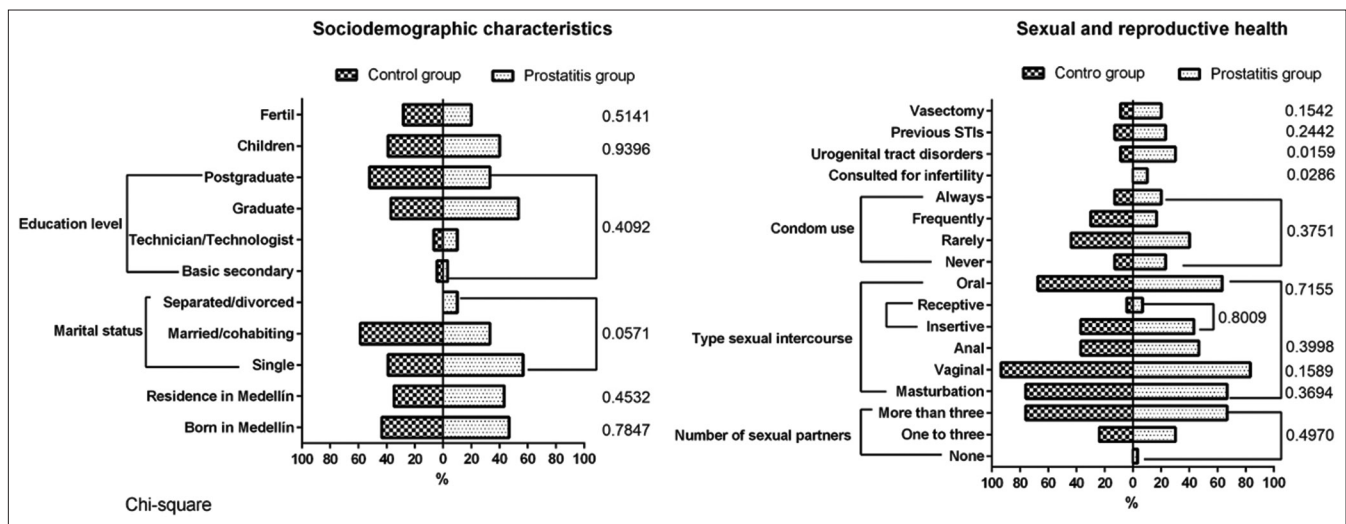


Figure 1: Chronic prostatitis, sociodemographic variables, and sexual and reproductive health

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 nitrites in serum samples than men with prostatitis (3.16 μM vs. 2.16 μM , $p = 0.0380$). 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

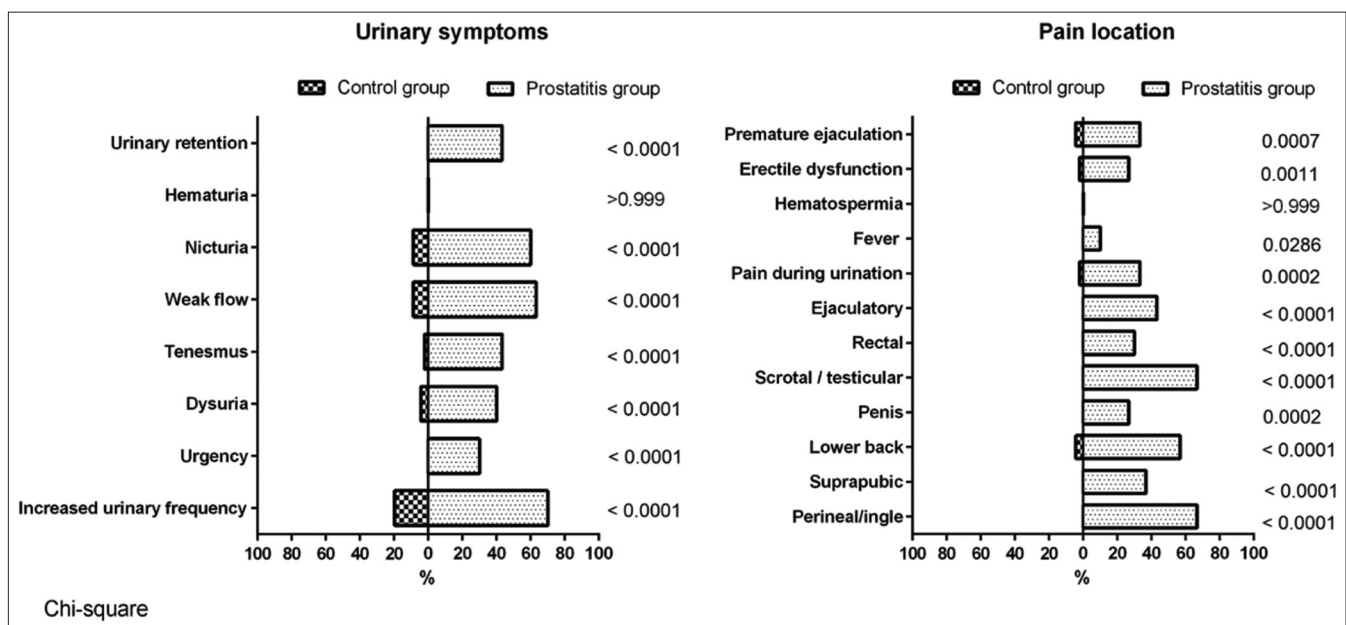


Figure 2: Urinary symptoms and pain location

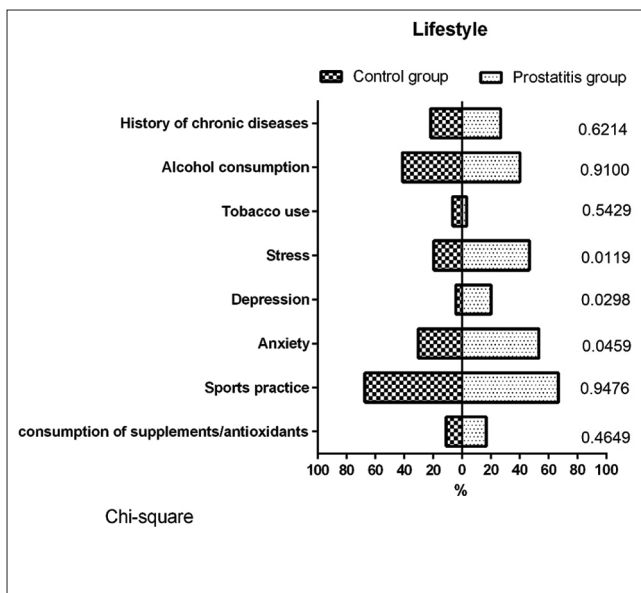


Figure 3: Lifestyle impact on chronic prostatitis

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

	Control group	Chronic prostatitis group	p value
Volume (mL)	2.75 (0.3–7.5)	2.50 (0.8–11.8)	0.7451
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 (10.0–290.0)	77.5 (0.0–520.0)	0.4561
Viability (%)	79.5 (36.0–92.0)	82.0 (43.0–85.0)	0.4970
Normal morphology (%)	5.8 (4.0–13.0)	4.4 (2.0–8.0)	0.0497
Teratozoospermia index	1.26 (0.96–1.5)	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 (8.5–84.4)	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 (2.1–98.5)	70.8 (14.9–96.9)	0.0473
Nitric oxide in serum (μM)	3.16 (0.07–17.1)	2.16 (0.23–7.48)	0.0380
Nitric oxide in plasma (μM)	0.95 (0.07–14.65)	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 care 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 synthase 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

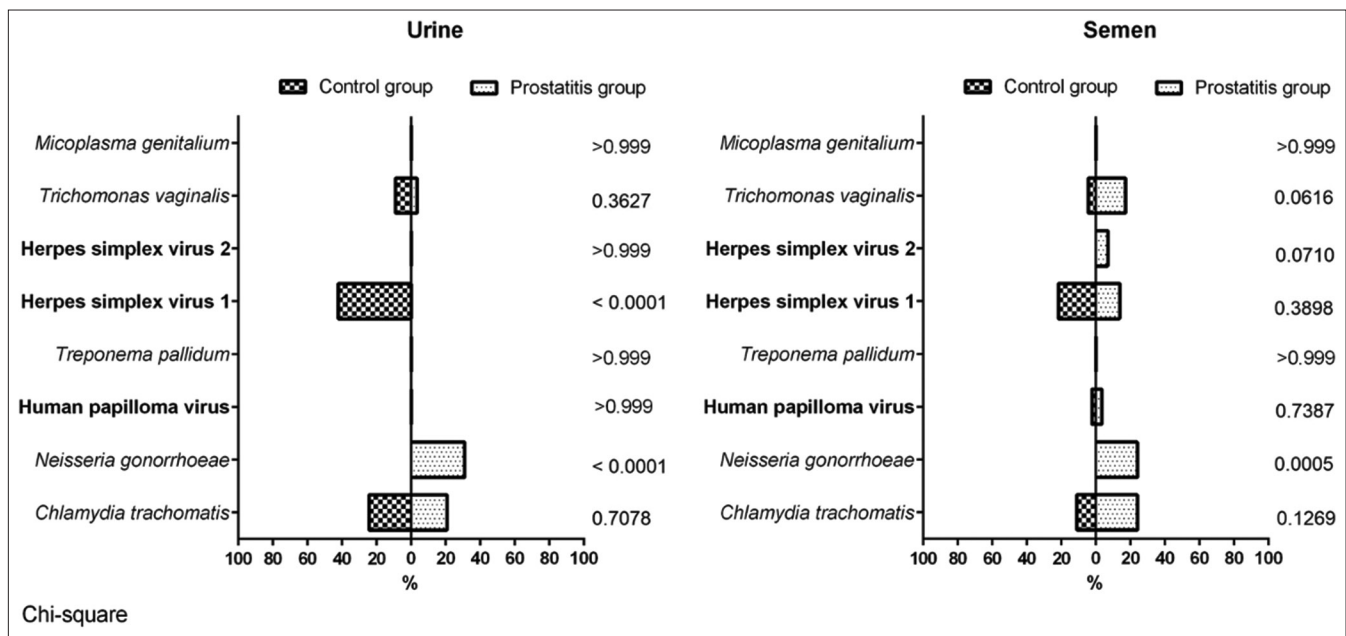


Figure 4: Sexually Transmitted infections DNA detection

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 (3.16µM 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

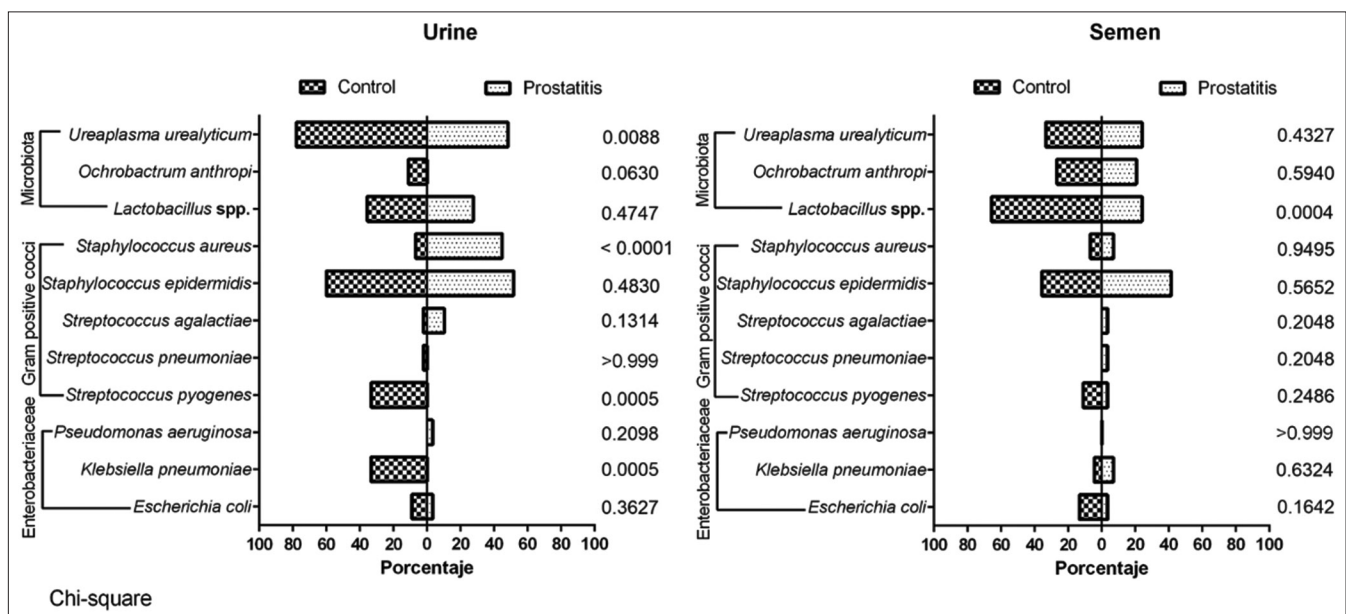


Figure 5: DNA detection of other bacteria associated with prostatitis

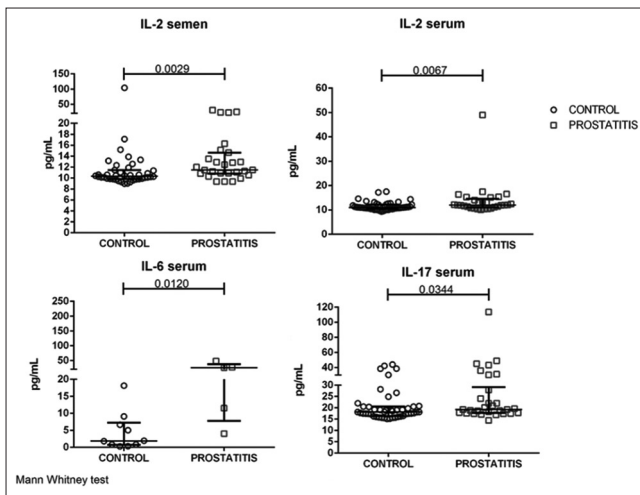


Figure 6: Inflammatory cytokines detection in volunteers with chronic prostatitis symptoms

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 $TNF-\alpha$ in prostatic fluid and semen has been considered a marker of inflammation in chronic pelvic pain syndrome and chronic prostatitis; it activates the $NF-\kappa\beta$ pathway inducing the expression of inflammatory factors such as $TNF-\alpha$ itself, IL-1 β 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-1 β , and $TNF-\alpha$. 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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