Short Communication

Study of Immunological Parameters as Diagnostic Markers in Patients with Chronic Prostatitis

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Abstract

Background: Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is the most frequent urologic condition in men under the age of 50. It is characterized by a wide range of painful and inflammatory symptoms in the lower back, testes, rectum, scrotum, perineum, and pelvis. **Objectives:** The study aims to investigate the role of immunological and inflammatory parameters in the diagnosis of CP. **Materials and Methods:** This case–control study involved a population of CP patients and healthy individuals. Forty samples were collected from patients suspected of CP according to their clinical manifestations, with ages ranging from 17 to 62 years. Patients were diagnosed by specialist physicians. In addition, 50 venous blood samples were taken from apparently healthy individuals as a control group. The study was carried out during the period from December 2022 to June 2023 in the urology and microbiology departments at the College of Medicine, University of Babylon, and Hilla Teaching Hospital. **Results:** The mean age of patients was 35.57 ± 8.81 years, and that of control subjects was 33.24 ± 9.55 years, and there was no significant difference between patients with CP and control subjects in mean age ($P = 0.236$). Mean levels of serum interleukin-8 (IL-8) were 133.17 ± 12.40 and 63.94 ± 8.67 in patients with CP and healthy control subjects, respectively; there was a highly significant increase in patients with CP in comparison with healthy controls. Mean levels of serum monocyte chemoattractant protein-1 (MCP-1) were 981.05 ± 65.51 and 1318.74 ± 80.15 in patients with CP and healthy control subjects, respectively; there was a significant decrease in MCP-1 levels in patients with CP in comparison with healthy controls. Mean levels of serum macrophage inflammatory protein-1 alpha (MIP-1α) were 269.59 ± 24.64 and 374.27 ± 21.99 in patients with CP and healthy control subjects, respectively; there was a significant decrease in patients with CP in comparison with healthy controls. **Conclusion:** The present results indicate IL-8, MCP-1, and MIP-1α are considered acceptable diagnostic markers.

Keywords: CPPS, IL-8, MCP-1, MIP-1α, prostatitis

Introduction

Prostatitis is the medical term for inflammation of the tissue of the prostate gland. It may happen as a necessary physiological reaction to an infection, or it may happen in the absence of an infection. It can be excruciatingly painful and distressing, but it usually improves with time. Prostatitis is a frequent urologic condition that many doctors find difficult to treat effectively. It is expected that up to half of all men will suffer from symptoms of prostatitis at some point in their lives.[1]

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is the most frequent urologic condition in men under the age of 50, characterized by a wide range of painful and inflammatory symptoms in the lower back, testes, rectum, scrotum, perineum, and pelvis. In most individuals, inflammation coexists with pain in the absence of an invasive infectious agent. The treatment options for patients are far from satisfying for either doctors or patients because the cause of CP/CPPS is still not completely understood.[2,3]

Access this article online

Quick Response Code:

Website: https://journals.lww.com/mjby

DOI: 10.4103/MJBL.MJBL_32_24

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Submission: 17-Mar-2024 **Accepted:** 04-Apr-2024 **Published:** 30-Apr-2026

How to cite this article: Al-Jobouri WAM, Al-Saadi MAK, Al-Marzook WAA. Study of immunological parameters as diagnostic markers in patients with chronic prostatitis. Med J Babylon 2026;23:785-9.

Chronic nonbacterial prostatitis/chronic pelvic pain syndrome (CAP/CAPS) is frequently linked to lower urinary tract symptoms, erectile dysfunction, and psychosocial issues, as well as pain in the lower back and abdomen. Furthermore, it has been discovered that CP/CPPS may have a major impact on male fertility.[2,4]

A number of theories have been proposed to explain the pathogenesis of CP/CPPS, including impaired urothelial integrity and function, cryptic infections, autoimmunity, endocrine imbalances, pelvic floor muscle spasm or tenderness, voiding dysfunction, peripheral and central sensitization and neuroplasticity, and psychosocial conditions.[5-7] Historically, it has been thought that CAP/CAPS is caused by infection; hence, it has been empirically treated with antibiotics, although with mixed results.[8] In a study by Hussein *et al*.,[9] prostate secretions were collected from 33 CP patients. Cultures of prostate secretions were found to include bacteria in 45.5% of cases. A total of 12.1% of the isolates were *Staphylococcus aureus*.

Many microorganisms, including *Mycoplasma hominis*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, *Ureaplasma urealyticum*, *Candida* spp., and the herpes simplex virus, have been linked to the condition. However, chronic inflammation and discomfort may continue even after the infection has been treated, presumably due to an autoimmune and/or neurogenic process. In susceptible males, infectious urethritis or prostatitis may serve as the first stimulus for chronic inflammation. If this were the case, the pathology would not be caused by infection, but rather, the infection would be the triggering factor.[10,11]

An increase rise in the number of leukocytes (granulocytes, macrophages, and T and B cells) is observed in semen and urine following prostatic massage or expressed prostate secretions (EPS). Also, in EPS, elevated amounts of inflammatory cytokines, immunoglobulins, chemokines, and mast cell mediators are found. Increased concentrations of Interleukin (IL)-1, TNF, IFN, IL-6, IL-8, monocyte chemoattractant protein-1 (MCP)-1/CC motif chemokine ligand 2 (CCL2), macrophage inflammatory protein-1 (MIP)-1/CC motif chemokine ligand 3 (CCL3), and lower concentrations of IL2R have been reported.[12] This study aims to study the immune response in patients with CP and the possible role of IL-8, MCP-1, and MIP-1α in the diagnosis of CP and used as diagnostic markers for CP.

Materials and Methods

Study design and patients

The present work was a case–control study involving a population of CP patients and healthy individuals. Full information was apparently taken from each subject. Forty samples were collected from patients suspected of CP according to their clinical manifestations, with an age range of 17–62 years, and 50 apparently healthy individuals as the control group. The study was carried out during the period from December 2022 to June 2023 at the urology and microbiology departments of the College of Medicine, University of Babylon, and Hilla Teaching Hospital.

Statistical analysis

Data were collected, summarized, analyzed, and presented using SPSS version 26 (SPSS Inc. Chicago, Illinois, USA) and Microsoft Office Excel 2010. Numeric data were presented as mean and standard deviation after performing Kolmogorov–Smirnov normality test and making decisions about normally and nonnormally distributed variables. Chi-square test was used to study the association between any two categorical variables.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with verbal and analytical approval from the patients before samples were taken. The study protocol, subject information, and consent form were reviewed and approved by a local ethics committee of Babylon Medical College, according to document number 78 in November 2022.

Results

The present study enrolled 40 patients with CP and 50 healthy control subjects. The mean age of patients was 35.57 ± 8.81, and that of control subjects was 33.24 ± 9.55 years, and there was no significant difference between patients with CP and control subjects in mean age (P = 0.236). The frequency distribution of patients with CP and healthy control subjects according to age was also shown in Table 1. Again, there was no significant difference in the frequency distribution of patients and control subjects according to age group (P = 0.113).

Table 1: Demographic characteristics of patients with chronic prostatitis and healthy control subjects

Characteristic	Patients, n = 40	Healthy control, n = 50	P
Age (years)			
Mean ± SD	35.57 ± 8.81	33.24 ± 9.55	0.236† NS
Range	17–62	23–55	
<30, *n* (%)	8 (20.0)	20 (40.0)	0.113¥ NS
30–39, *n* (%)	20 (50.0)	17 (34.0)	
≥40, *n* (%)	12 (30.0)	13 (26.0)	

NS: not significant at $P < 0.05$

†Kolmogorov–Smirnov normality test

¥Chi-square ($\chi 2$) test

The comparison of serum IL-8 levels in patients with CP and healthy control subjects has been carried out, and the results were demonstrated in Table 2. Mean levels of serum IL-8 were 133.17 ± 12.40 and 63.94 ± 8.67 in patients with CP and healthy control subjects, respectively; there was a highly significant increase in IL-8 in patients with CP compared to healthy controls ($P < 0.001$). The comparison of serum MCP-1 levels in patients with CP and healthy control subjects has been carried out, and the results are demonstrated in Table 3. Mean levels of serum MCP-1 were 981.05 ± 65.51 and 1318.74 ± 80.15, in patients with CP and healthy control subjects, respectively; there was a significant decrease in MCP-1 levels in patients with CP compared to healthy controls ($P = 0.013$). The comparison of serum MIP-1α levels in patients with CP and healthy control subjects has been carried out, and the results are demonstrated in Table 4. Mean levels of serum MIP-1α were 269.59 ± 24.64 and 374.27 ± 21.99 in patients with CP and healthy control subjects, respectively; there was a significant decrease in MIP-1α levels in patients with CP compared to healthy controls ($P = 0.002$).

Table 2: Interleukin-8 (IL-8) level in patients with chronic prostatitis and healthy control subject

Markers	Case–control comparison		*P*
	Patients, *n* = 40	Healthy control, *n* = 50	
Interleukin-8 (IL-8) level			
Mean ± SE	133.17 ± 12.40	63.94 ± 8.67	<0.001† HS
Range	10.62–280.30	4.40–219.78	

HS: highly significant at $P \leq 0.001$
†Kolmogorov–Smirnov normality test

Table 3: Monocyte chemoattractant protein-1 (MCP-1) level in patients with chronic prostatitis and healthy control subject

Markers	Cases-control comparison		*P*
	Patients, *n* = 40	Healthy control, *n* = 50	
MCP-1 level			
Mean ± SE	981.05 ± 65.51	1318.74 ± 80.15	0.013† S
Range	320.57–1994.23	157.46–2313.42	

S: significant at $P \leq 0.05$
†Kolmogorov–Smirnov normality test

Table 4: Macrophage inflammatory protein-1 alpha (MIP-1α) level in patients with chronic prostatitis and healthy control subjects

Markers	Cases-control comparison		*P*
	Patients *n* = 40	Healthy control *n* = 50	
MIP-1α level			
Mean± SE	269.59 ± 24.64	374.27 ± 21.99	0.002† S
Range	41.36–656.39	53.91–653.66	

S: significant at $P \leq 0.05$
†Kolmogorov–Smirnov normality test

Table 1 shows that the mean age of patients was 35.57 ± 8.81 and that of control subjects was 33.24 ± 9.55 years and there was no significant difference in mean age between patients with CP and control subjects in mean age ($P = 0.236$). Also, there was no significant difference in the frequency distribution of patients and control subjects according to age group ($P = 0.113$).

Table 2 shows that the mean levels of serum IL-8 were 133.17 ± 12.40 and 63.94 ± 8.67, in patients with CP and healthy control subjects, respectively; the level was significantly higher in patients with CP compared to healthy controls ($P < 0.001$).

Table 3 illustrates that the mean levels of serum MCP-1 were 981.05 ± 65.51 and 1318.74 ± 80.15 in patients with CP and healthy control subjects, respectively; the level was significantly lower in patients with CP compared to healthy controls ($P = 0.013$).

Table 4 shows that the mean levels of serum MIP-1α were 269.59 ± 24.64 and 374.27 ± 21.99 in patients with CP and healthy control subjects, respectively; the levels were significantly reduced in patients with CP compared to healthy controls ($P = 0.002$).

Discussion

The results of the present study were compatible with КОВАЛЫК *et al*.,[13] who found that the age of the included 287 males with underlying CP/CPPS ranged from 23 to 65 years (mean 37.1 ± 11.2 years). The majority of patients with CP belong to the age group 50–59 years 46 (69.0%), followed by the age group 60–69 years 25 (71.0%).[14] The mean age of the patient group (CP/CPPS) was 40.6 ± 2.1 (range from 30 to 52 years) years, and the mean age of the control group was 39.7 ± 1.8 (range from 33 to 50 years) years.[15] However, the study of Al-Hadrawi *et al*.[16] found that the mean age was 63.9 years, with the ages of 150 patients ranged from 30 to 99 years. Prolonged prostatitis affected 13.3% of the population.

Also, the study of Majzoub *et al*.[17] reported that according to the age distribution, 29 (48.3%) were prostatitis infertile and 13 (43.3%) were prostatitis fertile and were most common in the age group of 31 to 40 years. In the study by Sönmez *et al*.,[18] the mean age of patients with CP was 39.68 (± 10.15) years. The present study is consistent with the study of Motrich *et al*.,[19] who revealed that the mean age of the patients was 33.7 (22–48) years, while the mean age of the control group was 32.4 (24–48) years.

IL-8 is a potent inflammatory chemokine that predominantly acts as a neutrophil chemoattractant and

activating factor. It can also attract basophils and T cells. IL-8 appears to be substantially associated with prostate inflammation.[20]

The interpretation of high levels of IL-8 in CP patients compared to controls may be due to the fact that IL-8 plays an important role in the control and amplification of the immune response, as well as in the development of inflammation.[21]

The present study was compatible with,[22] which showed IL-8 concentrations in seminal plasma and EPS were considerably higher in males with CP/CPPS compared to controls.

Also, there is a compatibility with the study of Tyagi *et al*.,[23] which showed that compared to the controls, the seminal plasma from patients with CP/CPPS had noticeably greater levels of inflammatory cytokines such as IFN-y, IL-17, IL-1β, and IL-8. These findings showed a persistent inflammatory condition, likely brought by immunological responses to PAg in the male genital tract of CP/CPPS patients. In contrast with the present study, Liu *et al*.[24] found that compared to controls, IL-8 was considerably higher in CP/CPPS ($P < 0.05$).

Recent investigations have demonstrated the importance of CCL2 and CCL3 as biomarkers for IIIA and IIIB chronic pelvic pain symptoms, highlighting their potential clinical value in the diagnosis and management of prostatitis.[21]

Our result found that patients with CP/CPPS had higher CCL2 and CCL3 levels in their EPSs compared to controls. This result was incompatible with Murphy *et al*. who revealed that CCL2 was strongly linked with the white blood cell (WBC) count of EPS, CCL3 positively correlated with both the chronic prostatitis symptom index (CPSI) and the pain subscore.[25]

A study by Wong *et al*.[26] found that the level of CCL2 (MCP-1) and the severity of prostatitis were positively correlated.

The data from Desireddi *et al*.[27] suggested that CCL2 and CCL3, which resulted from prostate inflammation, are two chemokines that are known to lower the threshold of activation for neurons in the dorsal root ganglia (DRG), a sensory tissue in the peripheral nervous system, which leads to increased host susceptibility to neuropathic pain. This suggests that a complex chain of events, including microglial activation, has a role in the emergence and maintenance of chronic pelvic pain in prostatitis. Also, a study by Zou *et al*.,[28] revealed elevated MCP-1 chemokine levels in EPS from CPPS patients.

A potential biomarker for individuals with CPPS is the expression of CCL3 in EPS.[25] The present study was incompatible with Nishishita *et al*.,[29] showed that EPSs were obtained from 15 healthy participants and 23 patients with CP/CPPS. By using real time-polymerase chain reaction (RT-PCR) to amplify CCL3 messenger ribonucleic acid (mRNA) and enzyme-linked immunosorbent assay (ELISA) to determine CCL3 protein expression levels. CCL3 mRNA and protein levels were both noticeably higher than in the control group. The mRNA expression of MIP-1alpha was significantly higher in the CPPS IIIA and IIIB groups compared to the control groups ($P < 0.05$). MIP-1alpha protein levels were substantially greater in CPPS IIIA (1174.3 ± 89.2 pg/mL and in CPPS IIIB (842.3 ± 76.2 pg/mL) than in the control group (198.0 ± 37.8 pg/mL, $P < 0.05$).

After prostate massage, CCL3 levels rise in seminal plasma, EPS, and urine of CP/CPPS patients. Additionally, the prostates and spinal cords of models with chronic abacterial prostatitis exhibit elevated levels of CCL3. Significantly elevated CCL3 levels in the spinal cords promote interaction between neurons and glial cells, which induces macrophage migration and activates microglia, and the results showed a reduction in symptoms, proving CCL3 to be a key mediator of CP/CPPS.[21]

Zou and Liu[28] demonstrated a positive correlation between the severity of human prostatitis and CCL3 (MIP-1α) levels. While the study by Hussein *et al*.[30] indicated that tadalafil-treated mice produced less CCL3 (MIP-1) and CCL2 (MCP-1) compared to controls, it is possible that these cytokines could also be used as target indicators of a treatment impact.

Conclusion

The present results indicate IL-8, MCP-1, and MIP-1α are considered an acceptable diagnostic marker, depending on the findings of area under the curve.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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