Suez Canal University Medical Journal Vol. 28 (7), 2025
Pages 1-10

Erectile Dysfunction among Patients with Chronic Prostatitis/Chronic Pelvic Pain Syndrome

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Abstract

Background: **Erectile Dysfunction (ED) is the consistent inability to attain and/or maintain a penile erection sufficient for satisfactory sexual intercourse. ED is a very common condition that has a profound impact on quality of life and self-esteem. ED is believed to be due to many causes. Psychogenic, vascular, neurogenic, hormonal, cavernosal, iatrogenic, drug induced, and anatomic causes are thought to be involved in the pathogenesis of ED. Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) is a common clinical disorder that affects about 15% of men. It's characterized by pain or discomfort localized to the abdomen, pelvis, and genitals, as well as irritative and obstructive lower urinary tract symptoms (LUTS) in the absence of urinary tract infection.** ***The purpose of this review*** **is to explore the link between the ED and CP/CPPS conditions as it's thought that CP/CPPS is involved in the pathogenesis of ED.** ***Conclusion:*** **Men with CP/CPPS are at higher risk to have poor sexual functioning.**

Keywords: Erectile Dysfunction, Chronic Prostatitis/Chronic Pelvic Pain Syndrome, lower urinary tract symptoms

Erectile Dysfunction (ED)

Erectile Dysfunction (ED) is defined as the failure to achieve or maintain a rigid penile erection suitable for satisfactory sexual intercourse [(1)]. While no specific time period is part of this definition, some have suggested that the condition needs to persist for six months. It is a common condition in men over 40 years, with the prevalence increasing steeply with age and other co-morbidities [(2)]. ED can be a symptom of many underlying pathologies and is an important but underutilized cardiovascular risk factor. Any disease process which affects penile vessels, nerves, hormones, smooth muscle tissue, corporal endothelium, or tunica albuginea can cause ED. It is generally acknowledged that ED is closely related to cardiovascular disease, diabetes mellitus, dyslipidemia, and hypertension, among other disorders. Endothelial dysfunction appears to be the other common pathway in these patients [(3)].

It is difficult to obtain accurate values for the true prevalence of ED, as many patients fail to seek any medical attention and many physicians are reluctant to ask patients about their sexual health. The best available data indicates that 52% of men between 40 and 70 years of age suffer from ED [(4)].

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A meta- analysis of 24 studies involving 11,189 men was done to assess the prevalence of ED among Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) patients. Overall prevalence of sexual dysfunction in men with CP/CPPS was 62%, while the prevalence of erectile dysfunction and premature ejaculation was 29% and 40% respectively [5]. From 1999 to 2010, the prevalence of sexual dysfunction, ED and premature ejaculation was 65%, 27% and 41% respectively. From 2011 to 2014, the prevalence of sexual dysfunction, erectile dysfunction and premature ejaculation was 50%, 35% and 39% respectively [5].

Physiology of Erection

The critical process in penile erection activity is the relaxation of the intracavernosal smooth muscle. This permits increased blood flow into the corpora cavernosa which fills with blood and compresses the emissary veins, reducing venous outflow. Nitric oxide released by the cavernous nerve terminals initiates the erectile process while nitric oxide from endothelial cells acts to maintain it [6].

Nitric oxide stimulates the production of cyclic guanosine monophosphate (cyclic GMP) when it enters the smooth muscle. Protein kinase G is activated by cyclic GMP which opens potassium channels while closing calcium channels [7]. Low intracellular calcium causes the intracavernosal smooth muscle tissue to relax leading to increased blood flow with simultaneous veno-occlusive activity. This results in a rigid erection with minimal blood flow into or out of the corpora once the erection is obtained. The corporal smooth muscle contracts again when the cyclic GMP is degraded by penile phosphodiesterase and the process reverses. Pathology in any of the above processes can result in ED [7].

ED has a negative psychological impact on many patients, so they face many difficulties seeing a doctor. Physicians should ask obvious and direct questions to these patients while taking history. Good communication between the physician and the patients gives a great outcome [8].

Many male sexual function profiles and ED questionnaires have been developed. The most commonly referenced is the International Index of Erectile Function (IIEF) [9].

IIEF is statistically validated in many languages. Its 15 items address and quantify five domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. An abridged 5-item version of the IIEF-15 has been developed, in which 4 items are taken from the erectile function domain. The fifth item addresses sexual intercourse satisfaction. The most important difference between IIEF-15 and IIEF-5 is that the latter asks patients to self-assess erectile function and satisfaction over the past 6 months, a more clinically relevant and practical time frame than 4 weeks [9]. Initial treatment involves lifestyle modification. Recommended lifestyle modifications include: increased physical activity, healthy diet and/or nutritional counseling, cessation of smoking, drugs, and alcohol, good control of diabetes, lipids, and cholesterol. The patient's drug history should be carefully reviewed to remove or adjust the doses of any offending medications. Patients who have a psychological cause should be offered psychosexual therapy including the other partner [10].

Oral phosphodiesterase-5 inhibitors (PDE-5 inhibitors), such as sildenafil and tadalafil, are the first-line treatment of ED. They are effective in a lot of etiologies including cardiovascular disease, diabetes, and hypogonadism [11].

They act by decreasing the metabolism of cyclic GMP via phosphodiesterase inhibition, which increases the relaxation of cavernosal smooth muscle and cavernosal arterial blood flow. Sexual stimulation is required to release nitric oxide from the vascular endothelium and penile nerve endings to start the erectile process. PDE-5 inhibitors are highly effective and have an overall success rate of up to 76% [11].

Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS)

Chronic prostatitis remains an enigma for many physicians and patients. It is estimated that 15% of the male population are diagnosed with prostatitis with recurrence rates 50% in older patients [12]. The National Institutes of Health (NIH) developed a classification system based upon clinical syndromes, which replaced the old unvalidated diagnostic schemes that included such meaningless terms as 'non-bacterial prostatitis' and 'prostatodynia' [12]. Briefly, category I is an acute systemic infection, category II is recurrent urinary tract infection in a male with bacteria identified in the prostate between infections and category IV is asymptomatic prostatitis (inflammation found on biopsy or semen analysis) [12]. Type III or chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is defined as chronic pelvic pain not caused by other identifiable pathology that is often associated with genital pain, ejaculatory pain, abdominal pain, lower urinary tract symptoms (LUTS) and ED. It is CP/CPPS that provides the most annoying to patients and physicians [13].

CP/CPPS is a syndrome defined by chronic pelvic pain often associated with LUTS. Pain may be felt in the pelvis, lower abdomen, lower back and genitalia. Postejaculatory pain is common and often indicates pelvic floor muscle tension. LUTS include storage and/or voiding symptoms. Severe LUTS, especially with pain associated with voiding, should raise the possibility of painful bladder syndrome [13].

Physical exams should be focused on the genitourinary system to exclude other pathology, which can cause similar symptoms. During rectal exam, careful palpation of the pelvic floor muscles anterolateral to prostate often indicates spasm and tight knots or trigger points whose palpation will often reproduce the patient's primary pain. In evaluating these patients, it is important to know that no imaging or cystoscopic findings of CP/CPPS, only other conditions to be excluded [14].

A study of 48 healthy men and 60 men with chronic prostatitis demonstrated Staphlococcus aureus in semen. A more recent study analyzed VB 1, 2 and 3 in 110 CP/CPPS patients and 115 controls. They demonstrated a higher incidence of Burkholderia cenocepacia in the VB1 specimen in comparison to controls, however, the etiologic significance of this is unclear, and these studies continue [15].

Because CP/CPPS presents with diverse symptoms from likely multiple causes, a wide range of treatments have been studied. The most widely used categories of treatment include: antibiotics; anti-inflammatory medications; neuromodulators; alpha-blockers; pelvic

floor physical therapy (PFPT); and cognitive behavior therapy. one or all of these treatments are being used simultaneously as managed by the UPOINT clinical phenotyping system for much improved response [16].

Antibiotics are the first line therapy for many physicians. This may be due to the belief that an unknown causative organism may have a role in patients' symptoms [17]. When patients have identifiable bacteria in their prostatic fluid and evidence of chronic bacterial prostatitis, antibiotics, specifically fluoroquinolones and macrolides, can be effective in treating these bacteria and reducing symptoms, especially pain and sexual symptoms. In these studies, improvement rates were up to 70% in those patients [17].

In the absence of infection, repeated courses of antibiotics are not useful in CP/CPPS. Some patients may believe that they experience recurrent infections despite negative cultures because when they take antibiotics, their symptoms temporarily improve. This is likely because many of these antibiotics have anti-inflammatory properties. In-vitro studies of human endothelial cells have shown decreased expression of interleukin-6 and interleukin-8 with incubation of cells in ciprofloxacin [18].

Inflammation may cause some CP/CPPS symptoms. HSP70 expression is significantly lower and the inflammatory protein IL-1beta expression is higher in CP/CPPS patients when compared with controls. In a study of 463 men with diagnoses of CP/CPPS, 50% had >5 WBC per HPF in semen, this was statistically higher than the controls in whom 40% had such findings [19].

In an attempt to address this inflammation some have examined the use of anti-inflammatories, most of which failed to show considerable results. A study of 161 men randomized to either rofecoxib versus placebo showed some improvement in CPSI scores compared with placebo, but a significant percentage of patients did note an improvement in quality of life with treatment compared with placebo (56% vs 27%). oral prednisolone has been investigated and was not able to show any effect in a study of 21 patients [20].

Neuromodulating medications such as amitriptyline and gabapentin have been popular in the treatment of neuropathic pain, and studies are beginning to show their role in the treatment of CP/CPPS [21].

Alpha-adrenergic receptor blockers (alpha-blockers) are important treatment for the LUTS in patients with benign prostatic disease and used in CP/CPPS [22]. Alpha-blockers are used to improve urinary symptoms and studies looked at this separate from other pelvic symptoms. An initial randomized controlled trial of 60 men with CP/CPPS had significant improvements (32.9±5.27%) in International Prostate Symptom Scores, which was related to improvement in pain and quality of life measures, each of which improved by similar amounts. A similar randomized controlled trial in 91 patients assessing the effect of terazosin on urinary symptoms in CP/CPPS found significant improvements in voiding symptoms when compared to placebo [22].

It is well known that impaired dealing mechanisms negatively affect patients' reaction to any pain and response to treatment for that pain. This is true in patients with CP/CPPS as well and identifying this is important to improve

patients' quality of life. In a study of 80 patients, the presence of somatization or depression was associated with higher CPSI scores [23].

Cognitive behavioral therapy may help patients to deal with pain. Antidepressants such as duloxetine may also help as an adjunct to treatment, though it is not clear whether this is due to improvement in psychological symptoms or through another mechanism. This is an area of continuing research, but in a population with high rates of depression, offering psychological counseling should be a part of every physician treatment strategy [24].

CP/CPPS is a syndrome, not a disease, so patients may have a wide range of symptoms. This is likely the reason why large studies of monotherapy have consistently failed to show efficacy over placebo. CP/CPPS patients need to be appropriately delineated into clinically relevant category that can guide therapy. UPOINT system was developed to identify clinical phenotypes from which treatment strategies could be developed [25].

The UPOINT system that can be used to identify clinical phenotypes and direct therapy. In this system, each category has its own treatment. Urinary symptoms are treated with alpha-blockers or anticholinergics. Psychosocial symptoms are treated with psychological counseling and antidepressants. Organ-specific symptoms are treated with bioflavonoids, such as quercetin. Infections are treated with adequate courses of culture-directed antibiotics. Neurologic or systemic symptoms are treated with amitriptyline or gabapentin. Muscle tenderness is treated with a pelvic floor physical therapy and/or trigger-point injections [26].

CP/CPPS is a frustrating disease for many physicians and patients. Although it is not yet completely understood, we have made significant progress in its evaluation and treatment. Practitioners need to move away from the antiquated algorithms that commonly result in endless courses of antibiotics and embrace multimodality therapy that provides superior outcomes over other treatment strategies [27].

Association between ED and CP/CPPS

CP/CPPS is a complex disorder with unclear etiology. Its relationship with sexual dysfunction has often been overlooked. However, a growing body of literature suggests a high prevalence of sexual dysfunction in men with CP/CPPS. Men with CP/CPPS have reported problems including pain at ejaculation, pain during or after sexual intercourse, ED, decreased sexual desire, and premature ejaculation [28].

In the general population, ejaculatory pain is rare (1 % in one study) (29). However, ejaculatory pain is recognized as a common feature of men with CP/CPPS, and in some men, ejaculatory pain may be the only symptom of prostatitis [30]. In fact, ejaculatory pain has its own question on the NIH Chronic Prostatitis Symptom Index (NIHCPSI), question 2b, which asks, "In the last week, have you experienced pain or discomfort during or after sexual climax (ejaculation)?' [31]. During the creation of the NIH-CPSI, it was noted that ejaculatory pain was present in 58 % of patients compared to 17 % of patients with benign prostatic hyperplasia and 4 % of controls [31].

ED is a highly prevalent complaint among patients with CP/CPPS. Recent literature

has reported a prevalence of ED in patients with CP/CPPS of 15.0–40.5 % [32, 33, 34]. A 2008 study by Lee et al . investigated the prevalence of sexual dysfunction (self-reported erectile dysfunction, ejaculatory difficulty, or both) among a population of 296 men presenting with CP/CPPS. Patients scoring 21 or less on the International Index of Erectile Function (IIEF) were defined as having ED. Ejaculatory disorder was defined as including one or more of the following symptoms: ejaculatory pain, premature ejaculation, lack of interest in sexual activity, or difficulty reaching ejaculation [28]. According to the above definitions, 72.3 % of participants had self-reported sexual dysfunction. Of the patients with sexual dysfunction, 25.0 % complained of ED only, 33.4 % had ejaculatory difficulties only, while 41.6 % experienced both. Moreover, men with sexual dysfunction reported worse CP/CPPS symptoms and worse quality of life than men without sexual dysfunction [28]. A 2002 cross-sectional survey reported that men with CP/CPPS had worse erectile function as measured with the IIEF assessment tool and worse quality of life than men without prostatitis [35]. A recent case–control study looking at ED patients by Chung et al. [36] found that men with ED were more likely to have had a previous diagnosis of CP/CPPS (OR 3.62, 95 % CI) after adjusting for various demographic factors than compared with control patients.

Mechanism of ED in CP/CPPS

While there is evidence suggesting a link between CP/CPPS and ED, there is few literatures addressing the potential mechanisms underlying these two conditions [37]. ED usually has a multifactorial etiology, and organic, physiological, endocrine, and psychogenic factors are all involved. Here, we review possible associations between CP/CPPS and ED. The following relationships depends on patient age because of the increasing prevalence of ED in older men. Interest in the mechanisms of ED in the CP/CPPS patients would be focused on younger men who may be more likely to benefit from therapies of ED [38].

Most men with arteriogenic ED have impaired penile perfusion in the setting of systemic atherosclerotic disease. While common risk factors associated with arterial insufficiency such as hypertension, hyperlipidemia, and diabetes mellitus are less likely to be present in the young man with CP/CPPS, studies have shown that this population may still suffer from arterial inflow problems resulting in sexual dysfunction. A case–control study involving men with CP/CPPS showed that this group was more likely to have arterial stiffness associated with nitric oxide-mediated vascular endothelial dysfunction compared to asymptomatic controls [38]. Decreased arterial inflow may also be related to extrinsic compression from pelvic floor spasm. Up to 50 % of patients with CP/CPPS have signs of pelvic floor spasm on physical exam [39]. Pelvic floor physical therapy has been shown to significantly improve pelvic pain, urinary symptoms, and ED in these men [40]. Veno-occlusive dysfunction is another important cause of vasculogenic ED and is related to degenerative changes related to aging or traumatic injury [41].

No evidence showed a link between venogenic ED and CP/CPPS, and it is unlikely to be a prominent contributor to sexual dysfunction in the young male with CP/ CPPS. However, it is possible that Doppler sonographic parameters in a

patient with adrenergic vasospasm in the setting of high anxiety could lead to the incorrect diagnosis of veno-occlusive disease [42].

Hypogonadism is a common finding in men with ED. It's thought that sex hormones may also be an important factor in the development of prostatitis [43]. Thus far, evidence of a link between CP/CPPS and ED remains to be determined. Recent findings regarding the genetics of patients with CPPS suggest that an underlying problem with androgen regulation that may contribute to CP/CPPS. CP/CPPS patients have been found to have a different frequency of alleles near the phosphoglycerate kinase one gene, a region that is associated with familial prostate cancer, hypospadias, and androgen insensitivity [44]. Interestingly, another gene in the same region is the androgen receptor, thus raising the possibility of androgen insensitivity or dysfunction in the pathogenesis of CP/CPPS. In one small case–control study, CP/CPPS patients were found to have higher serum levels of androstenedione and testosterone and lower levels of cortisol as compared to controls [45].

It is estimated that 10–19 % of ED is neurogenic in etiology [43]. Because erection is a neurovascular event, any pathology affecting the brain, spinal cord, and cavernous/ pudendal nerves may lead to ED. Several mechanisms have been postulated regarding the neurologic basis of CP/CPPS that may also overlap with neurogenic ED. Patients with CP/CPPS are almost 5 times more likely than controls to have a history of neurological disease [43]. CP/CPPS patients have also been found to have abnormalities in the afferent and efferent autonomic nervous systems leading to neuropathic pain related to central nervous system sensitization. Interestingly, at a molecular level, several of the inflammatory markers and growth factors play a role in the neurologic basis CP/CPPS have also been found to be associated with ED although a clear mechanism linking the two conditions has yet to be defined [44, 46].

In addition to vasculogenic, endocrine, and neurogenic factors, psychological factors may also play a key role in the pathogenesis of ED in CP/CPPS. As is commonly seen with other pain conditions, CP/CPPS has a well-recognized association with stress, anxiety, and maladaptive responses to stressful situations [37]. Results from a 2008 case–control study show that, in addition to pain, many other psychological factors influence the sexual lives of men with CP/CPPS [47]. A statistically significant decline in erectile function was observed not only with increasing pain symptoms but also in men with worse stress appraisal. Additionally, frequency of sexual activity declined with increasing depression, and orgasm and pleasure/satisfaction from a sexual intercourse declined with worse stress appraisal and a greater non-belief in the relationship between emotions and pain. Studies have also demonstrated that CP/CPPS men have lower mental health scores compared to general population and also tended to have psychological adaptation problems related to depression, anxiety, hysteria, hypochondriasis, and somatization disorders [48]. The use of psychotropic medications in patients with both CP/CPPS and the above psychological co-morbidities may also be a significant contributing factor to ED in this population.

Conclusion

Sexual dysfunction in CP/CPPS represents a diverse spectrum of symptoms including ED, painful ejaculation, and premature ejaculation. The exact mechanism of ED in CP/CPPS patients remains unclear; however, recent research suggests a multifactorial association with vascular, neuromuscular, endocrine, and psychogenic etiologies. The literature regarding the relationship between ED and CP/CPPS is scarce and future work in this area would have significant impact on a clinical phenotype and proper treatment of CP/CPPS related ED.

Authors contribution

All authors contribute equally.

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