

REVIEW

PROSTATITIS: PREVALENCE, HEALTH IMPACT AND QUALITY IMPROVEMENT STRATEGIES

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Abstract: Since its identification as a discrete entity, prostatitis has been a crippling and dreadful disease for the males and from then till date it is well recognized that it has continuously eluded the urologists and the practitioners and the patients were generally avoided. But the newer advent in research has changed the concept of the medical management of prostatitis that had been in stagnation for the past many years. The traditional myths related to the disease were continued to be unlighted with improved understanding of the distribution, cause and measures for the management of this disease. From herbal treatment used by the ethnic communities historically to today's modern treatment modules of antimicrobial and anti-inflammatory agents, though not very successful, but has embarked a light of hope in both practitioners and patients for the effective management of this condition, which has negatively affected the normal as well as intimate life of the sufferers. With newer and more widely accepted classification of the disease the practitioners and patients diagnosed with prostatitis now can hope for a better improvement and management of the disease. The present study tries to encompass the important and useful work reported by several workers and progress in the effective management of this awful condition.

Keywords: prostatitis, prevalence, phytotherapy

Among the three accessory sex glands in males, the largest one and completely surrounding the urethra at the base of the urinary bladder is prostate gland. It is a walnut-sized composite gland, made up of 35 to 60 small, compound tubuloalveolar glands providing drainage to 20 or more ducts independently into the prostatic urethra. The bulk of the prostate is made by these small glands, which appear to form *strata* around urethra and consist of the periurethral mucosal glands, submucosal glands, and the main or principal prostatic glands, which lie peripherally. The prostate is encapsulated within a fibroelastic capsule vascular in nature that contains many smooth muscle cells in its inner layers. Broad septa extend into the prostate from the capsule and become continuous with the dense fibroelastic tissue that separates the individual glandular elements. The secretory units of the glands are irregular and vary greatly in size and shape, the lumina of secretory units may contain spherical bodies, the *prostatic*

concretions, which are supposed to result from condensation of secretory material. The glandular epithelium usually is simple or pseudo stratified columnar but may be low cuboidal or squamous in some of the larger saccular cavities, the epithelium differs from gland to gland and even within a single alveolus. The epithelium is limited by an indistinct basal lamina and rests on a layer of connective tissue that contains dense networks of elastic fibers and numerous capillaries. The cells contain abundant granular endoplasmic reticulum and many apical secretory granules. The concretions appear to increase with age and may become calcified. The connective tissue surrounding the individual glandular units contains numerous smooth muscle cells (a *fibromuscular stroma*), which aids in the rapid discharge of prostatic fluid at ejaculation. The prostatic secretion is a thin, milky fluid of pH 6.5 that is rich in zinc, citric acid, phosphatase, factors that enhance sperm motility, and proteolytic enzymes,

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one of which, fibrinolysin, is important in the liquefaction of semen. Prostatic secretion accounts for about one-third of the semen volume. The development and functional maintenance of the prostate is dependent on testosterone and its metabolites. Blood levels of prostate-specific antigen (PSA) produced by the prostate is an important factor in screening for prostatic size. Chronic pelvic pain syndrome (CPPS) or prostatitis is a disabling condition that may be accompanied with benign prostatic hyperplasia (BPH) or prostate cancer and affecting 10–14% of men of all ages and ethnic origin (1, 2). Nearly 50% of men at some point in their life suffer from this condition (3) yet most symptomatic cases do not have bacterial prostatitis, for which the treatment and management are usually victorious.

Advances in research are engraving the newer concept of the clinical management of prostatitis, which has not progressed for decades (4). A new overview of the historical perspectives surrounding the myths related to this disease has enhanced the understanding of the epidemiology of the syndrome and its significant complications for patients and for society. New research initiatives in etiology, pathogenesis, diagnosis, and treatment are being fueled by government funding agencies and an enlightened interest by the biomedical industry. Evolutionary increment with the beginning of new millennium offers urologists and patients diagnosed with prostatitis a new hope towards better improvement for this disease.

HISTORICAL ASPECTS

The recognition of prostatitis as a discrete entity clinically and pathologically dates back early in the 18th century (5). The underlying cause was assumed to arise secondarily to provocation of the prostate gland by alcohol, sexual indulgence, or violent exertion (predominantly horseback riding). Neisser A. (1882) asserted a close relationship between prostatitis and urethritis of gonorrheal infection. The acute stage of the disease often found to be fatal and may lead to the distressing problem of abscess formation. The first confirmative prostatic fluid analysis dates back to 1906 (6). The microbiologic background of most of the prostatitis was established in mid to late 1920s with result being backed by thousands of fluid prostatic fluid cultures (7–9). For decades, the bacterial cultures mostly Gram positive organisms and appearance of leukocytes in the prostatic fluid were the keen concern of the urologists (10–12). After 1940s, antibiotics along with prostate massage took strong hold of

treatment but previously treatment strategy was prostate massage only. Even though, the successful cure of symptoms in the majority of patients harboring chronic form of the syndrome continued to evade urologists. The period of 1950s enlightened the nonbacterial congested process possibly secondary to sexual extravagance or excessive masturbation as a reason behind the inflammation of the prostate (13), while the significance of leukocytosis and culture results, as well as the actual treatment results with antibiotics were doubtful (14, 15). A new era in understanding, diagnosing and treating prostate disease took birth after Meares and Stamey published their landmark work in 1968 (16). But the past three decade's researches made urologists slowly realize the shortcomings of the current classification, incapacibilities of diagnosis, and low quality treatment results. The current review is aimed at summarizing the work of various researchers towards the progress in treatment of this awful disease.

PREVALANCE

Prostatitis hits around 10–14% of men of all ages and racial origin (1, 2). Nearly 50% of men at some point in their life encounter this condition (3). An epidemiological case-control study focused on prostatitis categories II and III pursued by Bartoletti et al. (17) evaluated the prevalence and estimated the incidence and risk factors of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) in urological hospital outpatients in Italy. In his study, from January to June 2006, patients from 28 Italian urological centers ageing between 25 and 50 years with symptoms of CP/CPPS were consecutively enrolled. A total of 152 subjects of similar age, race and area of origin who were investigated for infertile couples but were otherwise healthy served as controls. In the study, out of 5,540 male urological outpatients 764 with CP/CPPS were enrolled, including 225 (29.4%) at the first presentation and 539 (70.6%) who underwent previous treatment. It was concluded that the prevalence of the syndrome was 13.8%, while the estimated incidence was 4.5%. Cigarette smoking, a high caloric diet with low fruit and vegetable consumption, constipation, meteorism, slow digestion, a sexual relationship with more than 1 partner and coitus interruptus were more likely in patients with CP/CPPS than in controls. The syndrome had a negative influence on libido, erectile dysfunction and premature ejaculation. Thus, it was concluded that the prevalence and estimated incidence of CP/CPPS in urological hos-

pital outpatients in Italy are high. The syndrome is closely related to lifestyle, diet, smoking, gastrointestinal or anorectal disease and impaired sexual function (17). Other reported studies concluded that 11% of Europeans had symptomatic prostatitis (1). Among urological outpatients in Canada with an average age of 50 years 2.7% were identified with prostatitis (18). Statistical data from the National Kidney and Urologic Disease Advisory Board (19) and the National Center for Health Statistics (20) showed that in the United States prostatitis was ranked fourth among the 20 principal diagnoses made by the physicians referring patients to urologists and 25% of urologic outpatient visits were due to chronic prostatitis symptoms (CPS). A prostatitis diagnosis was made yearly in 1–2 million people in the United States in men 18 years old or more including visits made to general practitioners (21). The prevalence was twofold greater in the south than in the northeast of the United States, with a useful finding that it did not vary by race. The study also reported that the diagnosis of prostatitis was made more frequently in 36–65 years-old men than in those aged 18–35, which is contradictory to previous reports indicating that prostatitis is more frequent in younger men (22, 23). China (22) and Korea (23), where prostate cancer is rare, were also among the areas of frequent diagnosis of this disease. Diagnostic frequency of CPS was higher in Canada where, following the pioneering work of Nickel, author of many articles and editor of a comprehensive book on prostatitis (24), there is an increased awareness of this syndrome. The prevalence of prostatitis-like symptoms in Chinese population has been reported to be 2.67%.

According to reports of Mehik et al. (25), 14% lifetime prevalence was reported in a cross-sectional Finnish study, in which 27% of Finnish men reported symptoms at least once per year and 16% complained of persistent prostatitis symptoms. In more than 90% of cases the origin of CP/CPPS is unknown. The remaining 5% to 10% of cases are bacterial, category II (17) but the bacterial role in CPPS is still argued (26).

The strong determinants include sex hormone levels, diet, previous genitourinary diseases, stress, psychological factors, allergy and marital status (1). The available treatment strategies mandate clinical evaluation (27).

CLASSIFICATION

To improve diagnosis and treatment of prostatitis, the National Institutes of Health (NIH) established

an International Prostatitis Collaborative Network. This group evaluated the literature and clinical practice and convened 2 consensus conferences (in 1995 and in 1998) to establish a new definition and classification of prostatitis syndromes. According to recommendations (28), prostatitis is classified into following classes with their definitions:

I. Acute bacterial prostatitis: It is an acute prostate gland infection.

II. Chronic bacterial prostatitis: It is a recurrent infection of urinary tract and chronic prostate gland infection.

III. Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS): It shows no definite infection. There is discomfort or pain in the pelvic region. It is further of two types on the basis of four glass test:

i) Inflammatory: Showing the presence of leukocytes in the semen, expressed prostatic secretions (EPS) or post prostate massage urine (29).

ii) Non-inflammatory: Showing no sign of inflammation in the semen, EPS or post prostate massage urine (29).

This sub categorization has not been found to be of any clinical or prognostic significance (30).

IV. Asymptomatic inflammatory prostatitis: Showing no subjective symptoms but leukocytes are found in prostate secretions or in prostate tissue while evaluation for other disorders (30). This is a histological diagnosis in patients undergoing a prostate biopsy (31).

Among the above categories, acute and chronic bacterial prostatitis account for approximately 5% to 10% of all cases of prostatitis (32). Both are undoubtedly associated with bacterial infection (often repeated) and a urine culture that grows uropathogens (33). However, most men diagnosed with prostatitis have pelvic pain without evidence of infection. Patients with category III prostatitis can be discriminated from those of I and II by the fact that they do not show any detectable infection of the prostate as cited by the conventional microbiologic techniques (29). Abnormalities in the EPS are the key objective features of category III prostatitis, and chronic pain is the key subjective indication. Most patients with chronic prostatitis are considered to be in category III (34).

Acute bacterial prostatitis

The causes of acute prostatitis are the urinary tract pathogens (35), which include: Gram negative organisms, most commonly *Escherichia coli*, *Proteus* spp, *Klebsiella* spp and *Pseudomonas* spp, Enterococci, *Staphylococcus aureus* due to prolonged catheterization and rarely anaerobic organ-

isms such as *Bacteroides* spp. This category is the simplest from the diagnosis point of view and the easiest to treat.

The mode of infection includes spread from the distal urethra/urethra, but can also spread from the bladder, blood and lymphatic system. Acute prostatitis is an uncommon complication of urinary tract infection (UTI) (31). The symptoms of acute prostatitis include dysuria, frequency and urgency, low back pain, perineal, penile and sometimes rectal pain, fever and rigors; arthralgia and myalgia may occur. Acute prostatitis is an acute severe systemic illness (36–38).

A detailed description of acute prostatitis can be found in United Kingdom national guideline for the management of prostatitis (31). Its treatment modules include empirical therapy consisting of oral or parenteral dosing of fluoroquinolones and β -lactam antibiotics (39).

Chronic bacterial prostatitis

This accounts for the bacterial infection of the prostate gland which is chronic and may be with or without symptoms of prostatitis. The historical background shows the presence of UTS recurrent in nature, which are caused by the same bacterial strain. It is infrequent in comparison to CP/CPSP (31). The most common bacterial infection accounts for *E. coli* (40). Among the Gram positive organisms, *Staphylococcus aureus* and *Enterococcus faecalis* may cause chronic bacterial prostatitis (41, 42). A more detailed description is provided in United Kingdom national guideline for the management of prostatitis (31). Fluoroquinolone therapy has been advocated as the best choice.

Chronic prostatitis /chronic pelvic pain syndrome

It is a frequent disease and its demographic study accounts for the greater percentage of work of the urologists. There were more outpatient visits for CPS than for BPH or prostate cancer (43). CPS has a very depressing impact on the patient's quality of life. According to Collins et al. prostatitis is the most important disease of the prostate gland for many patients (21). Also there is a lack of clear epidemiologic data on CPS due to the fact that there is no uniform definition of this ailment. Chronic prostatitis is more frequent than is commonly thought. According to Roberts et al. (1) one autopsy study (44) found a reported occurrence of 6.3% histological inflammation of the prostate, and another study (45) reported this figure to be 44%. CPSP is a frequent chronic condition varying between 2 and 14% lifetime prevalence (25, 46–48). A firm definition is not available

but a working definition includes the presence of characteristic symptoms of discomfort or pain in the genital or pelvic region exceeding 3 months within the past 6 months (49). CPSP remains to be of unidentified cause, possibly multifactorial. The various anticipated mechanisms include infection with no evidence showing that CPSP is due to sexually transmitted diseases (STD) (40, 50, 51), causes may also be categorized as autoimmune (52, 53) immunological (54–58) dysfunction of pelvic floor muscle or neuromuscular spasm (59, 60), increased prostatic pressure due to voiding dysfunction (61), functional somatic syndrome (62, 63), intraprostatic urine reflux (64–67). This observation has been confirmed directly by finding fine charcoal-like particles (histologically) and radio-opaque dye (radiologically) in the prostate and indirectly by the determination of urine components in prostatic secretion (chemically) (68), inflammation which is neurogenic (69) and chronic pain syndrome (70, 71). The majority of prostatitis cases fit in the definition of this category (34). Most of the authors have concentrated their work on this category.

HEALTH IMPACT

Chronic prostatitis severely impacts on the quality of life of patients and it has been stated that the quality of life of a patient with chronic prostatitis is comparable to that of a person who has sustained acute myocardial infarction or unstable angina or who has active Crohn's disease (72). The single question from the (American Urological Association) AUA-BPH symptom index, 7 "If you were to spend the rest of your life with your (genitourinary) condition just the way it is now, how would you feel about that?" allows patients to describe how distressed or happy they are with their present symptoms by rating the answer from "terrible" to "delighted." This question is a valuable and useful method by which the physician can quantitate and record quality of life aspects of the disease. The question was validated for chronic prostatitis as part of the process in developing the NIH-CPSI. Chronic prostatitis pain symptoms have a depressing impact on the lifestyle and mental well being of the sufferer (73). The pain can be very crippling in some sufferers and can impair one's quality of life. Chronic prostatitis has also been associated with erectile dysfunction (74).

TREATMENT MODULES

Today mainly antimicrobials, non-steroidal anti-inflammatory drugs and α -blockers are being

used. Unfortunately, results of many of these treatment modalities are subtle. The available treatment strategies for the prostatitis include the following:

1) Analgesics: Analgesics though used practically for most categories of prostatitis, there is limited evidence of their long-term efficacy. Subjective experience suggests that analgesics are not effective in patients with more painful syndromes. A possible reason being that the criteria applied for the chronic pain of prostatitis differ from criteria applied for other chronic pain syndromes, such as those accompanying malignancies (75). Anecdotal experience suggests that adding tricyclic antidepressants (such as amitriptyline) is helpful in controlling the pain associated with prostatitis syndromes (68).

2) Anti-infective agents: The effectiveness of antibiotics intravenous, oral or both in the cure of acute bacterial prostatitis is generally acknowledged. But the therapy for chronic prostatitis remains a challenge. Trimethoprim – in combination with sulfamethoxazole or alone, was the agent of choice for many years for patients with chronic prostatitis in whom the cause was supposed to be bacterial uropathogens. However, the prospective seen in animal pharmacologic studies (76) was not supported in clinical trials, and continuing results with trimethoprim-sulfamethoxazole have remained poor, cure rates being between 15% and 60% (77–79). The quinolone therapy included norfloxacin (80), ciprofloxacin (81, 82) and ofloxacin (83–85) seems to be attractive with remarkable rate of bacterial eradication but there is absence of the long-term results in connection to recurrence and symptom eradication.

3) Anti-inflammatory agents: the drugs in the category of non-steroidal anti-inflammatory drugs such as nimesulide (86, 87) and indomethacin may give favorable results in some patients having non-specific inflammation. Immuno-modulators such as cytokine inhibitors or COX-2 inhibitors may be helpful, but exhaustive research trials are required before this approach can be recommended.

4) Muscle relaxants: Muscle relaxants such as diazepam and baclofen are helpful in patients with category III B chronic pelvic pain syndrome, especially if sphincter dyssynergia or pelvic floor/perineal muscle spasm is confirmed (88). Nevertheless, the evidence is anecdotal only, and such medications have not been subjected to clinical scrutiny in terms of prospective clinical trials.

5) α -Blockers: Only scant amount of evidence is available suggesting that concomitant use of α -blockers with antimicrobials may improve the symptoms of and relapse of category III prostatitis

but the study analysis was cumbersome (89). α -Blockers find space in some cases when prostatitis is supposed to be secondary to dysfunctional voiding with (category IIIA) or without (category IIIB) intraprostatic ductal reflux. In such cases blocking of the α -receptors in the bladder neck and prostate theoretically may relieve some of the symptoms of prostatitis over time by improving flow parameters. Studies are available which are small and not well controlled with alfuzosin (90), phenoxybenzamine (88) and terazosin (89, 90) suggesting that clinical improvement is seen in 48 to 80% of patients. A 12 to 14 week trial of α -blocker is advocated to be reasonable (39).

6) 5- α -Reductase inhibition: The association of prostatic inflammation with the glandular epithelium depicts it to be under some sort of hormonal control. By promoting the degeneration of ductal and glandular tissue in the prostate, 5- α -reductase inhibitor (i.e., finasteride) shows the potential to improve flow parameters, reduce intraprostatic reflux and possibly even influence inflammation (91). A number of small pilot studies (92–94) support the theory that finasteride may favorably influence inflammation, voiding and pain associated with category IIIA chronic pelvic pain syndrome.

7) Phytotherapy: Various herbal drugs used by the ancient ethnic communities have been reviewed by Mukherjee and Singh (95). In Africa, infusion of *Barosma betulina* has been the folk medicine for prostatitis (95). North American Indians use *Podophyllum peltatum* for prostatitis. The utilization of plant extracts as a therapy for male disease, including prostatitis is of great economic business. In theory, phytotherapy may include 5- α -reductase activity, anti-inflammatory effects, and useful effects on voiding parameters, or may exhibit a placebo effect. Phytotherapy are believed to work by exerting anti-inflammatory effect, compounds in particular include quercetin and cernilton (39). Promising studies have been conducted extensively regarding a pollen extract, which is one such compound and shows promise (96, 97). Steenkamp et al. studied antibacterial, anti-inflammatory and antioxidant activity of 5 herbal plants *Pygeum africanum*, *Agathosma betulina*, *Hypoxis hemerocallidea*, *Epilobium parviflorum*, *Serenoa serrulata* (98) in the treatment of BPH and prostatitis with promising results. However, a rigorous prospective evaluation of these compounds is required before they can be opted as standard prostatitis therapy.

8) Pentosan polysulfate: Pentosan polysulfate is the only U.S. FDA approved oral medication available for the treatment of interstitial cystitis also

known as painful bladder syndrome. According to several investigators, many cases of prostatitis are sometimes the misdiagnosed cases of interstitial cystitis. It is so because of the resemblance between interstitial cystitis in women and prostatitis in men (99, 100). Wedrén in a double blind randomized study demonstrated that pentosan polysulfate has been found to be efficacious in some patients with chronic prostatitis but this effect needs to be studied in future investigations (101).

9) Allopurinol: It has been used in the management of gout and relieves it by inhibiting xanthine oxidase. The inflammatory response, according to some researchers, is due to refluxing of urate into the prostate (102), the fact being supported by one of the studies (103) showing positive results of allopurinol in comparison to placebo, with an outcome that a 3-month trial of allopurinol was suitable. However, additional evaluation (104) of the results of above trial is not supportive in the context of the beneficial effects of allopurinol, suggesting the widespread use of this drug in the treatment of chronic prostatitis as unfruitful.

10) Hormonal therapy: Some studies are available which show that finasteride has possible effect in CP/CPPS but trials are small, inadequately controlled, but in contrast to this other trial studies suggest inadequacy of this single therapy (105).

11) Heat therapy: Thermotherapy in the form of transurethral heat application (106–109) and hyperthermic transrectal application of heat (110–113) showed constantly favorable effects (prolonged) in some patients. The only obstacle lies in patient identification the best treated with this invasive procedure. Heat treatment may accelerate the natural healing process of long term inflammation but intraprostatic sympathectomy may result due to notorious effects of heat.

12) Massage therapy: It has been the ancient therapy for the ailment. But it no longer survived with the introduction of culture methods for lower urinary tract. This form of treatment was abandoned in the late 1960s when apparently better antimicrobial regimens in 1960s became available. However, currently it is reincarnating popularity, mainly because of the unfruitful results of standard medical therapy in patients sustaining chronic prostatitis. Its mechanism of action is believed to be clearance supposedly occluded prostatic ducts, improving circulation and antimicrobial dissemination (114).

13) Surgical treatment: Surgery is required in case of CPS when a specific indication is discovered. Patients having obstruction in bladder neck verified urodynamically may require transurethral

incision of the bladder neck (110). Other surgical procedures include retrograde transurethral balloon dilation of the prostate gland (115, 116), radical transurethral resection of the prostate (117, 118) and prostatectomy for patients with infected calculi have been indicated.

14) Palliative therapy: Along with the medication, supportive therapy, including biofeedback, relaxation exercises for stress management, changes in the lifestyle (i.e., diet changes, discontinuing bike riding, horse riding), acupuncture, massage treatment, chiropractic therapy, meditation, yogic exercises and even simple habits such as sitting on ring cushions or soft donuts, alter positively in combating symptoms and more or less provide support patients to live and manage with disease.

In one of the studies, anti nanobacterial therapy has been proposed for the treatment of CPPS with significant improvement (119).

Though antimicrobials are dominantly used in prostatitis, an important study cites that the majority of cases of prostatitis fit within the definition of chronic pelvic pain syndrome, for which routine antibiotic use is not indicated. The study shows that evidently antibiotics are not effective in the majority of men with CPPS, but they were prescribed in 69% of men with this diagnosis with conclusion that 7-fold higher rate of usage of fluoroquinolones necessitates the strategies to avoid unnecessary usage of antibiotics in men with prostatitis (120).

CONCLUSIONS

The present review is aimed to summarize the available studies done by several authors on prostatitis. Prostatitis is a crippling condition and the negative impact on a patient's quality of life is not inferior to what a patient experiences when suffering from myocardial infarction, unstable angina or active Crohn disease. The disease is related to multiple causes such as diet, lifestyle, diseases of the gastrointestinal and anorectal tract.

It is clear that the time, resources, finance, and scientific scrutiny, which are being used on research and management of prostatitis, are not sufficient enough to make the urologists and other clinicians to tackle the disease in an efficient manner.

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