



## Prostatitis: Recent Update on Etiopathogenesis, Molecular Diagnosis and Role in the Genesis of Benign Prostatic Hyperplasia (BPH) & Prostatic Carcinoma (Pca)

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### Abstract

Prostatitis is a common problem in elderly. Prostatitis is caused by implantation of gram negative organism by direct route or lymphohematogenous route, instrumentation, inoculation of BCG for bladder cancer & occasionally as a part of military tuberculosis involving genitourinary system. Prostatitis can lead to different clinical symptoms like fever, chill, UTI, low back pain, erectile dysfunction and sometimes in long standing cases can lead to BPH & Pca. Diagnosis of prostatitis specially that of chronic abacterial prostatitis may be sometimes difficult and this can create a problem for the patient & the physician. So there is need to identify early molecular markers apart from routine microscopical, culture & sensitivity on prostatic smear and radiology & imaging and biopsy tests. The present review article is based on search on different web site, Pubmed, online journals describe recent update on different types of prostatitis, its etiopathogenesis, role in the development of BPH & Pca and early molecular markers. These will lead to a better understanding on prostatitis, open some more research avenues and help in defining better management strategies.

**Keywords:** Prostatitis; Etiopathogenesis; Role in BPH & Pca; Molecular markers

### Introduction

Prostatic lesions are common problem for males of increasing age. Only three pathologic processes affect the prostate gland with sufficient frequency to merit discussion: inflammation, benign nodular enlargement, and tumors. Prostatitis may be divided into several categories; acute and chronic bacterial prostatitis, chronic abacterial prostatitis, and granulomatous prostatitis [1]. Although prostatitis is much less than that of BPH and Pca but still is important for its varied clinical presentation, increased morbidity, difficulty in exact early diagnosis and sometimes treatment failure leading to longterm management. Prostatitis is also important for its longterm complications like development of BPH and Pca in some cases. Different types of prostatitis, their etiopathogenesis, molecular mechanisms and genesis in the development of BPH and Pca are discussed below on the basis of search on different online portals and some text books.

### Acute prostatitis

Acute bacterial prostatitis usually results from bacteria similar to those that cause urinary tract infections. Thus, most cases are caused by various strains of *E. coli*, other gram-negative rods, enterococci, and staphylococci. The organisms become implanted in the prostate usually by intraprostatic reflux of urine from the posterior urethra or from the urinary bladder, but occasionally they seed the prostate by lymphohematogenous routes from distant foci of infection. Prostatitis sometimes follows surgical manipulation of the urethra or prostate gland itself, such as catheterization, cystoscopy, urethral dilation, or resection procedures on the prostate. Clinically, acute bacterial prostatitis is associated with fever, chills, and dysuria. On rectal examination the prostate is exquisitely tender and boggy. The diagnosis can be established by urine culture and clinical features [1].

The symptoms, investigation & treatment modalities are varied among acute prostatitis admitted in urology, infectious disease, internal medicine & geriatric departments. Those who are admitted in urology department presented with bladder outlet obstruction, received a blockers & anti-inflammatory drugs. Those who are admitted in infectious disease department presented with fever & received longer & more appropriate antibiotic. In geriatric department patients presented with cognitive disorder and post voidal urine volume measurements. In internal medicine patients

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presented with wide range of symptoms and had very diverge investigations and antibiotic regimen. Overall 3:1 ratio of community acquired acute prostatitis to nosocomial acute prostatitis. Culture yielded *E.coli* in (58% of acute prostatitis 68% community acquired a acute prostatitis) [2].

Sometimes acute bacterial prostatitis may occur due to rare human pathogen like *raultella planticola* [3], *Listeria monocytogenes* [4], *Pseudomonas aeruginosa* [5]. One study compared the clinical and microbiological characteristics between bacterial prostatitis and transrectal biopsy related acute prostatitis. The researchers reviewed the record of 135 patients admitted in hospitals for acute prostatitis in 2013. They concluded a higher incidence of septicaemia and antibiotic resistance bacteria in transrectal biopsy related patients then spontaneous acute bacterial prostatitis patients [6].

Another study by Ludwig M [7] concluded acute prostatitis does not seem to represent a major diagnostic therapeutic problem as long as prostatic abscess formation is present. Acute bacterial prostatitis is common in patient population who are at high risk include those with diabetes, cirrhosis, suppressed immune system [8]. Depending on history of previous antibiotic use, clinical pictures, Microbiological features, resistance pattern of the isolate it is advocated that prompt initiation of effective treatment is essential to decrease morbidity and mortality in hospital admitted patients of acute bacterial prostatitis specially after transurethral ultrasound guided biopsy of prostate [9].

Another form of acute bacterial prostatitis is caused by Extended Spectrum Beta Lactamase (ESBL) Producing *E. coli*: A study of 1339 hospital admitted patient who reached imipenem finally after not responding to usual treatment with ciprofloxacin 500 mg BD for 5 days. It emphasises prompt initiation of effective antimicrobial therapy especially with ESBL producing *E.coli* based on knowledge of local distribution of pathogen & their susceptibility [10]. Since 2006 ESBL strain is increasing and presence of ESBL showed more detrimental effects on clinical course of the patients resulting in higher rate of progression rate to chronic prostatitis [11] for early diagnosis of acute prostatitis. Diagnostic & prognostic value of acute prostatitis depend on blood culture was evaluated blood culture was positive in 21% of patients [12]. Other diagnostic tests like urinary leukocyte esterase and Nitrite dip test for acute prostatitis maybe tried [13] for early diagnosis of acute prostatitis.

### Chronic bacterial prostatitis

Chronic bacterial prostatitis is difficult to diagnose and treat. It may present with low back pain, dysuria, and perineal and suprapubic discomfort. Alternatively, it may be virtually asymptomatic. Patients often have a history of recurrent urinary tract infections (cystitis, urethritis) caused by the same organism. Because most antibiotics penetrate the prostate poorly, bacteria find safe haven in the parenchyma and constantly seed the urinary tract. Diagnosis of chronic bacterial prostatitis depends on the demonstration of leukocytosis in the expressed prostatic secretions, along with positive bacterial cultures. In most cases, there is no antecedent acute attack, and the disease appears insidiously and without obvious provocation. The implicated organisms are the same as those cited as causes of acute prostatitis.

### Chronic abacterial prostatitis

Chronic abacterial prostatitis is the most common form of prostatitis seen today. Clinically, it is indistinguishable from chronic bacterial prostatitis. There is no history, however, of recurrent urinary

tract infection. Expressed prostatic secretions contain more than 10 leukocytes per high power field, but bacterial cultures are uniformly negative. The etiology and pathogenesis of nonbacterial prostatitis which accounts for 90-95% of cases is largely unknown. Protein biomarkers like SOD3 and CA1 are identified as potential diagnostic, marker for non bacterial prostatitis. In a study by (Yan x etal 2015) they have validated more than 160 samples from various categories of non bacterial prostatitis (III, a, II b, IV) and matched healthy controls found two zinc binding protein superoxide dismutase 3 (SOD3) and carbonic anhydrase 1 (CA1) were significantly higher in all types of prostatitis than control.

### Granulomatous prostatitis

Extra Pulmonary Tuberculosis constitutes 20-25% of all System. Only 27% of Extra Pulmonary Tuberculosis Causes genitourinary system [14]. Prostate gland is affected in 2.6% [15] characterized by the presence of tuberculous granuloma with Langhans giant cell in the prostate. Although TB seems to be a rare disease 77% of men who died of tuberculosis of all conditions had prostate TB mostly contacted during their life time [16]. Some studies suggests that prostate TB like any other chronic inflammation may predispose prostate cancer [17].

Granulomatous prostatitis may be specific, where an etiologic infectious agent may be identified or non specific. The most common cause is related to installation of BCG within the bladder for treatment of superficial bladder cancer. BCG is an attenuated mycobacterium strain that gives rise to a histologic picture indistinguishable from that seen with systemic tuberculosis. However, in this setting the finding of granulomas in the prostate is of no clinical significance, and requires no treatment. Fungal granulomatous prostatitis is typically seen only in immunocompromised hosts. Nonspecific granulomatous prostatitis is relatively common and represents a reaction to secretions from ruptured prostatic ducts and acini. Although some of these men have arecent history of urinary tract infection, bacteria are not seen within the tissue in nonspecific granulomatous prostatitis.

Administration of Bacillus calmette-Guerin (BCG) has been shown to cause granulomatous prostatitis mistaken for prostate cancer [18,19]. Malignant diseases like mantle cell lymphoma involving the prostate can features as granulomatous prostatitis [20]. Infectious granulomatous prostatitis is uncommon and most cases of granulomatous prostatitis are classified as nonspecific granulomatous prostatitis [21,22]. Apart from histopathology granulomatous prostatitis can be diagnosed by MRI, PET Scan with increased FDG activity (Flusine 18 flurdeoxyglucose) [23-26].

**Fat, impaired metabolic syndrome and prostatitis:** Fat and insulin could have a detrimental effect on prostate health boosting inflammation. This indirect link between metabolic syndrome and chronic inflammation fat boosts, while androgen receptor activation counteracts BPH associated prostate inflammation [27]. One review article focused on the role of HFD in the genesis of oxidative stress, intra prostatic inflammation and their influences on signaling pathways that orchestrate various prostate diseases, including cancer and Oxidative stress in BPH [28].

### Chemokine and prostatitis

A variety of chemokines are actively secreted by prostatic microenvironment causes disruption in tissue hemostasis. The accumulation of senescent stromal fibroblasts and possibly epithelial cells may serve as potential driving force behind chemokine secretion in the ageing enlarged human prostate. This is mediated by MAPK

(mitogen activated protein kinase) and P13K (Phosphoinositide 3 kinase) Jignalling which is responsible for cellular proliferative response [29]. Studies suggest that cytokine family might be associated with BPH & Pca. Immunology showed immune staining for IL17A, IL17RA, IL17E, IL17F was significantly elevated in prostatic tissue for BPH and Pca compared to that of control with increased human of inflammatory cells and CD 31+ blood vessels [30].

### Zinc and prostatitis

Prostatic zinc accumulation is connected with secretory function of prostate and zinc concentration present in prostatic of diseases differs greatly from normal level [31]. They reviewed systemic literature serches as pubmed, embase, CNk1 science direct/Elsevier, and cochrane library upto March 2015 and found that the zinc concentration in prostatic fluid and seminal plasma from chronic prostatitis were significantly higher than normal controls.

### Sexual dysfunction & prostatitis

Men with symptomatic benign prostatic hyperplasia and erectile dysfunction had significant inflammation of the prostate to cause spurious increase of PSA level and results in unnecessary biopsy [32,33]. Asymptomatic prostatic inflammation in men with clinical BPH and erectile dysfunction affects the predictive value of prostatic specific antigen [34].

### Prostatic & BPH

Chronic prostatic inflammation seems to play a crucial role in BPH pathogenesis & progression. Several data favors the role of lymphocytes infiltration in the development of prostatic adenoma as an effect of self monitoring remodeling process [35].

Chronic prostatic inflammation would lead to tissue damage and continuous wound healing thus contributing to prostatic enlargement. (Gandaslia G, 2013) (Kapral SA, 2016) Several different stimuli may induce chronic prostatic inflammation which in turn would lead of tissue damage and continuous wound healing thus contributing to prostatic enlargement [36,37].

### Prostatitis & Pca

Infection or inflammation of the prostate (prostatitis) may increase the chance for prostate cancer while another study shows infection may help prevent prostate cancer by increasing blood to the area. In the particular, infection with the sexually transmitted infections Chlamydia, gonorrhea, or syphilis seems to increase risk. Finally, obesity and elevated blood levels of testosterone may increase the risk of inflammation and subsequently prostate cancer [38-40].

### Conclusion

From the literature reviewed it is evident that prostatitis is one of the most common urological problems interms of morbidity and its longterm complication can lead to BPH and Pca in some cases, although the evidence is not compelling. Diverse in its clinical manifestation, etiology, treatment modalities has laid the importance of early & proper diagnosis of prostatitis and its effective treatment. As most of the non bacterial prostatitis which accounts for 90-95% of the cases, the etiology is largely unknown estimation of serum protein can be a potential diagnostic marker in this setting. Serum protein SOD3 and CA1 and zinc estimation, different cytokine can also be very helpful to understand the etiopathology of prostatitis, along with radiology & imaging techniques like USG, MRI, culture & sensitivity, Histopathology of prostate & DPRE can be combinedly used for acute diagnosis & better management for prostatitis. These

will lead to define better strategies for early diagnosis of different types of prostatitis and can reduce the morbidity from it & prevent progression to BPH & Pca.

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