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Inflammation and Benign Prostatic Hyperplasia

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Introduction

Prostatitis, a histological diagnosis, has evolved over the years to describe a clinical syndrome that was believed to be associated with prostatic inflammation. Similarly, benign prostatic hyperplasia, another histological diagnosis, has evolved to describe a clinical syndrome believed to be associated with prostatic enlargement. Recent explorations of the interrelationships between these prostate associated histological and clinical conditions have generated a lot of interest and excitement. The purpose of this review is to describe these relationships and their impact on the management, in particular, of BPH.

Definitions

BPH is correctly defined as enlargement of the prostate gland from the progressive hyperplasia of stromal and glandular prostatic cells [1]. Clinical BPH refers to the lower urinary tract symptoms (LUTS) associated with benign prostatic enlargement (BPE) causing bladder outlet obstruction (BOO). Clinical prostatitis can be divided into acute and chronic bacterial prostatitis (NIH Category I and II), rare infectious diseases of the prostate gland, the much more common chronic prostatitis/chronic pelvic pain syndrome (Category III chronic prostatitis/chronic pelvic pain syndrome or CP/CPPS) and asymptomatic inflammatory prostatitis (Category IV) [2]. Histological prostatitis refers to the confirmation of prostate inflammation by microscopic examination. Asymptomatic prostate inflammation would be categorized as Category IV. See Table 1 for definitions and classifications of these various BPH and prostatitis conditions.

Lack of Association of Histological Prostatitis and Clinical Prostatitis

Traditionally, prostatitis has referred to a clinical condition associated with infection and/or inflammation of the prostate. The clinical diagnosis of a symptomatic prostatitis syndrome is made on the basis of clinical symptoms, some clinical findings, culture results and in some cases demonstration of inflammation in prostate fluid (expressed prostatic secretions or post prostatic massage urine). While this concept does hold true for bacterial prostatitis (Categories I and II) confirmed with specific bacterial cultures, it may not be as simple in the much more common Category III Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS).

An examination of the 488 men enrolled into the National Institutes of Health Chronic Prostatitis Cohort Study (NIH-CPC Study) determined that leukocytes in the prostate specific specimens (expressed prostatic secretions [EPS] or post prostatic massage urine specimens [VB3]) did not correlate with any specific symptoms or symptom severity [3]. The

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inflammatory status (leukocyte counts in EPS and/or VB3) in a total of 463 men enrolled in the NIH CPC study were compared to 121 age matched control men without any urinary or pain symptoms [4]. Men with CP/CPPS had significantly higher leukocyte counts in these specimens (50% and 32% had 5 or more, or 10 or more white blood cells per high power field in EPS, respectively) than asymptomatic men (40% and 20% respectively). The high prevalence of leukocytes in the asymptomatic control population certainly raised questions about the clinical relevance of inflammation detected by our current diagnostic tools. A small scale study [5], which examined correlations between the symptoms and histology of prostatitis in biopsies of men with a clinical diagnosis of CP/CPPS suggested that histological inflammation may not be a significant factor in the disease process. Of the 97 patients examined, just 33% had histological evidence of inflammation, with only 5% having a moderate or severe grading.

An examination of 5,597 men with biopsy and clinical evaluation of prostatitis-like symptoms (completion of chronic prostatitis symptom index [CPSI]) enrolled in the REDUCE study [6] provides the largest body of data examining relationships between symptoms of chronic prostatitis and histologic prostate inflammation. The study population consisted of aging men with an elevated PSA level, but with a negative prostate cancer biopsy, recruited as an 'at-risk' group for the development of prostate cancer [6]. Chronic histologic inflammation was found in more than 78% of men in REDUCE [7], reflecting its almost ubiquitous nature in aging men. Acute inflammation was found in 16.5% of the study population, and when present was almost always graded as mild. Data from this analyses of REDUCE population failed to establish substantive links between the CPSI and the presence of histologic inflammation. In men with acute inflammation, no correlations between total or component CPSI scores, including presence of prostatitis-like symptom complex, and inflammation were observed. For those with chronic inflammation, a weak but statistically significant association was observed between inflammation status and total CPSI score, but no significant relationships with pain were observed. From a clinical perspective, presence of chronic prostatitis-like symptoms did not provide any discriminative value for a histologic diagnosis of either acute or chronic inflammation.

Association of Clinical Prostatitis and BPH

BPH is a disease of ageing men [1] An estimated 42% of men 51 to 60 years of age have histological BPH. The incidence increases to over 70% in men 61 to 70 years of age and to almost 90% in those 81 to 90 years of age. The prevalence of LUTS associated with BPH parallels that of pathological BPH; > 50% of men over 50 are believed to experience LUTS secondary to an enlarged prostate gland.

Prostatitis has traditionally been considered a condition which inflicts younger men, but it is apparent that it is as common in older men [8]. Compared to men aged 51 and higher the odds of a documented prostatitis diagnosis is only 2-fold greater in younger men [9]. Approximately 8% of men over 50 years of age report at least some mild prostatitis-like symptom in the past week compared to 11% of younger men [10]. Little attention has been given to the association between BPH and prostatitis, despite the high prevalence of both conditions in ageing men.

Many physicians have trouble clinically distinguishing prostatitis from BPH in the older male population [11]. In 1992, 31,681 United States health professionals without prostate cancer provided information on urological diagnoses and lower urinary tract symptoms [12]. 57.2% of the 5,053 men with prostatitis also reported a history of BPH while 38.7% of the 7,465 men with BPH reported a history of prostatitis.

Clinical BPH is characterized by voiding LUTS. Prostatitis is characterized primarily by pain. Pain and/or discomfort on ejaculation is one of the most common and bothersome symptoms,

but also the most differentiating symptom experienced by men with chronic prostatitis [13]. Painful ejaculation has been reported by approximately 5% – 31% of men with LUTS related to BPH in both community and clinic populations [14–18].

There is no doubt that the clinical syndromes of prostatitis and BPH can coexist. But is the diagnosis of clinical prostatitis at a young age a risk factor for development of later BPH. A population based sample of 2447 men residing in Olmsted County, Minnesota were evaluated to determine whether physician diagnosed or self-reported prostatitis were associated with development of clinical BPH or related outcomes [19]. Physician diagnosed prostatitis was associated with a 2.4 fold increased odds of receiving a later diagnosis of BPH. Men with a history of prostatitis were also more likely to receive treatment for BPH compared to men without prostatitis. A diagnosis of prostatitis may be an early marker for later development of BPH.

Association of Inflammation and Clinical BPH

Histological inflammation can be demonstrated in the majority of BPH pathological specimens [20–23]. For years, the importance and clinical relevance of these seemingly asymptomatic inflammatory infiltrates were only speculated upon.

REDUCE (REduction by DUtasteride of prostate Cancer Events) is an ongoing, large scale, 4-year clinical trial designed to determine if and to what extent the dual 5 α reductase inhibitor dutasteride reduces the risk of biopsy-detectable prostate cancer compared with placebo in men at high risk of developing prostate cancer [6]. The entrance criteria for REDUCE Study, included the requirement of a prostate cancer-negative biopsy prior to enrollment. The data from the entrance biopsy have enabled additional protocol-defined investigations to be made, including examination of the baseline relationships between histologic prostate inflammation and lower urinary tract symptoms (LUTS; measured with the International Prostate Symptom Score [IPSS]) in over 8,000 men. Using a modification of the histologic classification of prostatitis proposed by Nickel et al [24] a central pathology laboratory (Bostwick Laboratories, Richmond, VA, USA) graded average acute and chronic inflammation across all biopsy cores on a 4-point scale (none [0], mild [1], moderate [2], or marked [3]) based on average cell density and extent of tissue involvement in each biopsy core.

Given that the mean prostate volume in men enrolled in the REDUCE study [6] was 46 ml and the PSA 5.8 ng/ml, it is likely that histologic BPH is common in the REDUCE population. As would be expected, chronic histologic inflammation was found in more than 78% of men in REDUCE [25]. Statistically significant but clinically small increases in IPSS symptoms were noted in men with inflammation compared to those without (e.g. Wilcoxon rank-sum test for differences in Total IPSS by presence vs absence of maximum chronic inflammation unadjusted $p < 0.0001$). Similarly, statistically significant correlations were found between average chronic inflammation score and the IPSS variables. However, the magnitude of these correlations was small, indicating very weak associations. The clinical relevance of the small, but statistically significant difference in IPSS in patients with and without chronic inflammation and the statistically significant, but weak associations between chronic inflammation and IPSS demonstrates a consistent pattern, that inflammation in BPH may be important.

If inflammation is indeed associated with BPH symptoms, anti-inflammatory agents should be investigated as new targets for the pharmacological treatment of BPH. Given the fact that nonsteroidal anti-inflammatory drugs (NSAIDs) are well known for their ability to decrease pain and inflammation, the effectiveness of ibuprofen together with the alpha- blocker, doxazosin, on BPH was evaluated for their efficacy in decreasing the expression of JM-27, a protein particularly expressed in the prostate that appears to be highly up-regulated in

symptomatic BPH [26]. This study showed that doxazosin as well as ibuprofen significantly decreases cell viability and induced apoptosis in BPH prostate cell lines. In addition it decreased the expression of JM-27. Unfortunately there is very little good data available to assess the clinical response of anti-inflammatory therapy in BPH. A single center, unblinded trial randomized 46 men with LUTS and BPH to receive rofecoxib (a COX-2 inhibitor) 25 mg/day plus finasteride 5 mg/day versus finasteride 5 mg/day alone for 24 weeks [27]. The study found that while there was not a significant difference between symptom improvement at 24 weeks, there was a statistically significant advantage of the combination therapy compared to finasteride alone in a short-term interval (4 weeks). It was hypothesized that the association of rofecoxib with finasteride induced a more rapid improvement in clinical results until the effect of finasteride becomes predominant. Phytotherapy has become one of the most popular treatment modalities for BPH. One of the primary mechanisms of why these herbal agents work is the anti-inflammatory effects of the various herbal preparations [28]

Role of Inflammation in the pathogenesis of Histological BPH

Three recent reviews on the pathogenesis of BPH have provided an evidence based thesis that strongly suggests a role of inflammation in the propagation of histological BPH [29,30,31]. Kramer and Marberger [31] have recently outlined the current state of knowledge in regard to the influence of inflammation on the pathogenesis of BPH. Chronic inflammatory infiltrates, mainly composed of chronically activated T cells and macrophages frequently are associated with BPH nodules [20,32,33]. These infiltrating cells are responsible for the production of cytokines (IL-2 and IFN γ) which may support fibromuscular growth in BPH [34]. Immigration of T cells into the area is attracted by increased production of proinflammatory cytokines such as IL-6, IL-8 and IL-15 [30,35,36]. Surrounding cells become targets and are killed (unknown mechanisms), leaving behind vacant spaces that are replaced by fibromuscular nodules with a specific pattern of a Th0/Th3 type of immune response [37].

What we do not know is why the leukocyte population increases in BPH. A number of hypotheses have been generated based on recent basic research. In-situ studies demonstrated elevated expression of pro-inflammatory cytokines in BPH. IL-6, IL-8 and IL-17 may perpetuate chronic immune response in BPH and induce fibromuscular growth by an autocrine or paracrine loop [37,38] or via induction of COX-2 expression [39]. Immune reaction may be activated via Toll-like receptor signalling and mediated by macrophages and T cells [38]. Conversely, anti-inflammatory factors such as macrophage inhibitory cytokine-1 [40] may be decreased in symptomatic BPH tissues. Animal models provided evidence for the presence of unique T-cell subsets which may suppress autoimmunity in healthy Sprague–Dawley rats resistant to chronic nonbacterial prostatitis [41]. Based on the available scientific evidence, that it is highly likely that age-dependent weakening of the immune system, coupled with modified hormonal secretion, leads to the deterioration of a postulated population of suppressor cells that actively suppresses the recognition of prostatic antigens which leads to gradual infiltration of the prostate by lymphocytes and subsequent cascade of events that leads to BPH [42].

Impact of Inflammation on Progression of Clinical BPH

An examination of baseline prostate biopsies in a subgroup of 1,197 patients in the Medical Therapies of Prostatic Symptoms (MTOPS) study found that there was a chronic inflammatory infiltrate in 43% of the men [43]. It was hypothesized that the presence of histological inflammation may be a predictor of progression. There was a very clinically significant difference in the progression rate based on the presence or absence of inflammation. Patients in all groups (placebo, finasteride, doxazosin and combination finasteride and doxazosin) with inflammation were more likely to progress clinically in terms of symptoms, AUR or BPH

related surgery. For those with no inflammation, there was overall clinical progression in 13.2% of patients, while 3.9% had BPH-related surgery and none had AUR; corresponding values for those who had chronic inflammation were 21% ($P=0.08$ vs no inflammation), 7.3% (not significant) and 5.6% ($P=0.003$). Chronic inflammation accounted for every AUR event in this subgroup of patients with prostate biopsies, while in patients with no inflammation there was no AUR.

The observation that the presence of prostatic inflammation may be clinically relevant in terms of prediction of BPH related progression is very important. The 4 year longitudinal follow-up of the 8,000 men enrolled in the REDUCE trial [6,7,25] may confirm this finding. Many of the men enrolled in the REDUCE trial would have had BPH at baseline (predicted by baseline high mean IPSS scores, elevated PSA and negative initial biopsy). The baseline histological status of these men are documented and progression data in terms of BPH symptom and event (surgery and AUR) progression will be collected. A further important point is that inflammation may also have an important role in the pathogenesis of prostate cancer [44] and that particular association will become very clear when the REDUCE trial is completed.

Biomarkers for Inflammation in BPH

If inflammation is associated with the pathogenesis, symptoms and progression of BPH, then a biomarker would be invaluable. There are a number of early candidates and many others are currently being assessed by international research groups.

A small study [45] suggested that measurement of serum malondialdehyde (MDA), an index of inflammation and oxidative stress, may be a useful marker in BPH. Serum MDA levels were analysed in 22 BPH patients and 22 healthy donors showed an increase in levels in the BPH patients and a positive correlation with PSA (used here as a marker of prostate hyperplasia). To our knowledge this association has not been replicated.

The association of serum C-reactive protein concentration, a nonspecific marker of inflammation, and lower urinary tract symptoms (LUTS), suggestive of BPH, was examined in 2337 men who participated in the Third National Health and Nutrition Examination Survey between 1988 and 1994 [46]. They found that men with a C-reactive protein concentration above the limit of detection (>3.00 mg/l) were 1.47 times more likely to have three or more symptoms than men with a C-reactive protein concentration below the detection limit (not statistically significant).

Cytokines and chemokines, inflammatory mediators are believed to be important in the pathogenesis of prostate inflammation. Increased expression of IL-8 is noted in BPH tissue culture [47] which by direct and indirect mechanisms could promote proliferation of non-senescent epithelial and stromal cells thus contributing to the increased tissue growth seen in BPH. Such processes may lead to the discovery of potential biomarkers for prostate inflammation in BPH. Seminal plasma levels of eight cytokines and nine chemokines were evaluated in 83 men (20 healthy controls, 9 men with CP/CPPS IIIA [inflammatory], 31 with CP/CPPS IIIB [non-inflammatory] and 23 men with BPH) [48]. Prostate specimens from 13 BPH patients were analysed to detect interleukin 8 (IL-8) producing cells and to characterize inflammatory infiltrates. IL-8 concentration in seminal plasma was positively correlated with symptom scores in both the CP/CPPS patients and BPH patients.

Although a number of potential markers (C-reactive protein, IL-8, markers of oxidative stress) have been evaluated, these markers are generally nonspecific for prostate or BPH. However, it opens the search for biomarkers that could be used to stratify patients as to risk of developing BPH or related BPH adverse outcomes, monitor symptoms and response to medical therapy for BPH.

Conclusion

Inflammation in the prostate gland appears to more closely related to BPH than the clinical syndrome chronic prostatitis. A translational approach to research (bed to bedside) should unlock the mysteries of this association [Figure 1]. Further understanding of the role of inflammation in BPH and clinical detection of this inflammation will expand our understanding of BPH pathogenesis, its histological and clinical progression, allow risk stratification for patients presenting with BPH related LUTS and suggest novel treatment strategies.

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Figure 1.

A bidirectional translational research approach (bench to bedside) will eventually improve our understanding of the association of inflammation with BPH and result in better stratification of patients for risk assessment and focused treatment.

Table 1
Definitions and categorization of histological and clinical benign prostatic hyperplasia and prostatitis

Type	Benign Prostatic Hyperplasia		Prostatitis	
	Histological	Clinical	Histological	Clinical
Definition	enlargement of the prostate gland from the progressive hyperplasia of prostatic cells	the lower urinary tract symptoms associated with benign prostatic enlargement	Microscopic evidence of prostatic inflammation	Prostate/pelvic pain syndrome
Subcategories	Glandular Stromal	LUTS – lower urinary tract symptoms BPE- benign prostatic enlargement BOO – bladder outlet obstruction	Acute Chronic	Cat I - Acute Bacterial Cat II - Chronic Bacterial Cat III - Chronic Pelvic Pain Syndrome