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BENIGN PROSTATIC HYPERPLASIA (K MCVARY, SECTION EDITOR)

Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms: What Is the Role and Significance of Inflammation?

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Abstract

Purpose of Review The purpose of this review is to summarize the role and significance of inflammation as a putative additional factor contributing to lower urinary tract symptoms and the progression of benign prostatic hyperplasia. We review (1) the histologic definition of prostatic inflammation and its prevalence, (2) the effects inflammation in the prostate including on risk of acute urinary retention, and (3) the effects of systemic inflammation on the prostate and on voiding.

Recent Findings Inflammation is a highly prevalent finding in the prostate, both on a histological and biochemical level. Men with inflammation have higher IPSS scores and increased prostate size; however, these differences appear to be imperceptibly small. Men with inflammation do experience a significantly increased risk of developing acute urinary retention, an event that is associated with significant morbidity. Recently, attempts have been made to identify more specific biochemical markers of local inflammation, and to identify regional patterns of inflamed tissue within the prostate which may be associated with higher IPSS scores, accelerated progression, and AUR. The effects of systemic inflammatory states, most notably MetS, and their role in LUTS have also been examined.

Summary Inflammation is a common finding in prostates of aging men, but its contribution to lower urinary tract symptoms and benign prostatic hyperplasia progression appears to be small when considered as a clinically relevant entity. Advances in the understanding of different forms of inflammation, and their impact when experienced in different locations within the prostate, may refine this knowledge. Systemic inflammation affects voiding, including in the absence of a prostate, but again significant effects of systemic inflammation on the prostate itself are also difficult to demonstrate. Prostatic inflammation is associated with a significantly increased risk of acute urinary retention.

Keywords Prostatic inflammation · Benign prostate hyperplasia · Lower urinary tract symptoms · Inflammation

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Introduction

BPH is a common affliction of mankind, impacting the lives of millions of men through its causative role in LUTS and increasing in prevalence with age. Worsening LUTS and the event of urinary retention are associated with significantly increasing risks of mortality [1, 2]. In both the USA and globally, the healthcare system cost burden of this disease process are well into the billions of dollars per year. However, the factors that underlie this heterogeneous and variable hyperplasia remain poorly defined. Regardless of the physical size of the gland itself, the most common pathway that causes men to seek care, receive medication, or undergo surgery is urinary symptoms.

The likelihood of undergoing surgery or of developing a significant measure of symptoms as defined by the International Prostate Symptom Score (IPSS) increases with

both total and transition zone gland size, and removal of excess tissue bulk results in significant and durable symptom improvement [3–6].

The causative agents and factors of BPH/LUTS are multifactorial and incompletely understood. Evidence for a two-factor model exists, those factors being bulk growth (hyperplasia and hypertrophy) and adrenergically driven smooth muscle tone; the presence of a third factor, inflammation, has been proposed [7, 8]. Our goal is to review the clinical data supporting inflammation in this disease process and specifically to assess the impact on the clinical endpoints of gland size, as measured by imaging study such as ultrasound, computerized tomography (CT) or magnetic resonance (MRI), and on symptoms as reflected by the validated IPSS score [9].

A number of systemic disease processes have been suggested to be associated with BPH/LUTS, including metabolic syndrome, diabetes, and especially the hormonal changes that accompany obesity. We will explore the latest thought and data regarding the impact of inflammation, both that which is localized to the prostatic itself as well as that which is systemically evident, against the impact of BPH/LUTS.

Inflammation Is Common in the Prostate

Inflammation has been identified as a common finding in tissue associated with BPH. In 1979, 162 sequential patients undergoing transurethral resection of the prostate (TURP) for BPH/LUTS, 98% were observed to have histologic inflammation [10]. Review of resected tissue from prostates that had symptoms deemed severe enough for surgery revealed the universal presence of varying histologic inflammation in a population with a high prevalence of preoperative catheterization [7]. No correlation to prostate size, prostate tissue bacterial infection or catheterization was seen. Using different microscopic criteria, other researchers found presence of inflammation in 43.1% of 3942 prostates, with moderate or severe inflammation making up 22% of that group [8]. A positive correlation was seen between increasing size of prostate and presence of inflammation, with nearly 80% of the glands in the largest size category demonstrating inflammation, mostly chronic, while the smallest size group (30–39 cc) showed only a 17% prevalence of any inflammation. All these patients had been identified as having symptoms that required surgery; no controls nor IPSS scores were available for these findings.

An important autopsy series of 167 prostates showed that, in true cross-sectional analysis, inflammation was more common in glands with BPH than those without (75% vs 50%, $p < 0.01$) and yet not more or less common when dichotomized into groups above and below their median size of 40 g (69% vs 56%, $p = 0.1$). [11] Additionally, inflammation, when present, was found confined to BPH nodules in up to 85% of these prostates. More recent work suggests that inflammation occurring in stromal vs non-stromal prostatic tissue compartments may be associated with clinical differences, including a 10-g difference in prostate size and higher voiding pressures [12•].

Effects of Inflammation Within the Prostate

Prostatic inflammation can be defined in a variety of ways. Most commonly has been the presence or absence of hematoxylin and eosin stained T cell and macrophage infiltrates, but other markers including inflammatory markers CD-4, CD-8, CD-45, and CD-68 as well as C-reactive protein, tumor necrosis factor, interleukin-6 and others have been evaluated [13••, 14]. In an attempt to codify histologic findings, a consensus definition for histological inflammation was developed in 2001 to standardize description of location, grade and extent [15]. To date, no direct relationship between these histologic categories and symptomatic expression has been reported.

Impact on Size As we have seen, prostatic inflammation is a common finding in men with BPH/LUTS who undergo surgery. Given the dependence on tissue from men who had experienced clinical progression of their BPH to the point of requiring surgery, it has been difficult to assess whether a similar prevalence of inflammation exists in asymptomatic men. Fortunately, controlled studies designed to assess the impact of medication on prostate growth and cancer have provided some insights into the prevalence, and the impact on growth, of inflammation. Two large studies stand out: the REDUCE trial was designed to assess the impact of dutasteride on incidence of prostate cancer over a 4-year interval; MTOPS looked at BPH progression over a similar time period of 4.5 years [16, 17]. Both of these large trials included baseline biopsies for all patients included, 1198 men in the MTOPS series and 8824 men in REDUCE, allowing assessment of the prevalence and 4-year natural history of inflammation in the biopsied regions of the prostate. Results suggest a correlation between presence of inflammation and an increase in measured size of 4.3 additional grams in the MTOPS study, and a 3.1-g additional size in the REDUCE placebo arm [18, 19].

Impact on Symptoms When looking at IPSS or other measures of progression, the impact of the presence or absence of inflammation in the prostate on symptoms has been difficult to identify at a clinically relevant level. IPSS symptomatic differences become perceptible by patients when they reach a difference of 3 or more: REDUCE patients evidenced a higher score by 0.6 IPSS points (8.8 vs 8.2) while the MTOPS patients showed no difference in IPSS scores [13••, 18, 20]. An interesting assessment of the impact of inflammation within the gland itself has been the studies done looking at changes in compliance in the prostatic urethra, suggesting that a fibrotic

response to immune cell activity could result in a stiffening of this segment that results in higher voiding resistance and that can presumably occur in the absence of glandular hypertrophy [21–23]. Presumably, inflammation occurring in this area would not be assessed by transrectal biopsy, leaving this open as a possible mechanism that may differ substantially from background: one study showed an IPSS difference of 4.0 (8.0 vs 12.0, $p < 0.05$) and a much higher rate of urodynamically significant obstruction, despite same-sized prostates [22].

In a retrospective review of over 1000 prostate biopsies performed before TURP for LUTS, 30% were read as having evidence of histologic prostatitis (significant stromal lymphocytic infiltrate) [24]. Stepwise volume-controlled analysis showed that symptoms were increased in the presence of prostatitis for glands under 50 ml volume, while in those patients with glands over 50 ml symptoms were influenced by increasing volume but not inflammation.

AUR

An important feature of this discussion is the recurring finding of an association between the presence of inflammation and an increased risk of acute urinary retention (AUR). AUR, as a stand-alone event, is associated with significantly higher mortality than in similar men without AUR [1]. The MTOPS database showed that 5.6% of patients with inflammation progressed to AUR, while none of the patients lacking inflammation had AUR [25]. Another study found that a higher proportion of TURPS done for AUR had inflammation present in the resected tissue, but also notes that these patients had a high prevalence of catheterization and infection before resection, possibly further contributing to the observed inflammation [26]. Following this work, Nickel and colleagues evaluated the role of inflammation in the placebo arm of the REDUCE trial [27]. Chronic inflammation was identified in 78.3% ($n = 3126$) of these men. These patients had an increased risk of developing AUR (HR 1.79 (1.31–2.44)). However, the presence of inflammation had no effect on the development or progression of BPH. A retrospective study of 428 TURP specimens showed that those with evidence of chronic prostatitis had a significantly higher preoperative IPSS (29.9 vs 23). Despite addressing their outlet obstruction, they had worse outcomes at 1 year than the group without prostatitis [28]. However, these results were again confounded by a higher rate of preoperative urethral catheterization in the group with prostatitis (24 vs 11%). More specifically, it appears that inflammation within the stroma of the prostate is the stronger risk factor for developing AUR [12•].

The aforementioned studies focus on histologic inflammatory changes observed on H&E staining. An innovative approach to defining inflammation is direct assessment of inflammatory markers including CD-4, CD-8, and others [13••]. The presence of only one of these markers was mildly associated with a 4-point or greater increase in IPSS (CD-4, HR = 1.86). However, CD-4, CD-8, and CD68 were all more strongly associated with the development of AUR (CD-4, HR = 3.08; CD-8, HR = 2.39; CD68 = 2.53). This again highlights the stronger association of tissue inflammation with risk of acute urinary retention, while the effects on long-term prostate growth or symptomatology remain less clinically apparent.

The Relationship of Systemic Inflammation to Voiding

Age, voiding, and systemic inflammation are intertwined in a complex fashion that involves local and distant organs. Effects of systemic medications that impact inflammation, and correlation of markers that indicate dysfunction, offer some insights into this study.

In between local prostatic inflammation and broad systemic inflammation lies a recent body of work that has added significantly to the understanding of the impact of prostatic obstruction and high-pressure voiding on the adjacent bladder. Investigators have identified pressure-responsive Nod-Like receptors in the urothelium, which when activated by Danger Associated Molecular Patterns (DAMPs) lead to formation of a so-called inflammasome, which subsequently activates inflammatory pathways in the bladder. This process appears to initiate a sustained inflammatory condition that results in LUTS, fibrosis and may ultimately culminate in bladder failure [29, 30•]. Further characterization of this pathway has potential to accelerate the understanding of the interaction between BPH, BOO, and LUTS.

NSAIDs

Data implicating NSAID-responsive LUTS, whether in observational studies or interventional trials, are disparate and one of the challenges in these data are separating the direct effect of the medication on the pathogenesis of LUTS from the underlying and presumably systemic inflammatory process that provokes the usage of the NSAIDS. Beginning in 1990, analysis of the Olmstead County cohort of men suggested that long-term usage of non-steroidal anti-inflammatories (NSAIDS), most commonly aspirin, resulted in a lower chance of LUTS or decreased flow rate [31].

Conversely, a population-based case-control study from the Netherlands suggested that NSAID usage was associated with a two times higher risk of acute urinary retention and analysis of the 4735 Prostate Cancer Prevention Trial placebo recipients found an increased risk of BPH with NSAID usage [32, 33]. Similarly, a population-based cohort of 75,000 Finnish men found the risk of BPH was significantly elevated among

NSAID users compared with non-users (HR 2.04, 95% CI 1.97–.21) [34]. This finding did not appear to apply to aspirin, which was noted to be generally used for prevention of vascular thrombosis and not relief of inflammation or pain. However, analysis of 4771 men in the prostate, lung, colorectal and ovarian cancer screening trial found no association between NSAID usage and 6 different clinical definitions of BPH/LUTS [35]. As noted above, separating the medication's usage, presumably for a systemically symptomatic inflammatory process that may be causative of LUTS, from any beneficial effect of the medication itself is difficult.

Interventional studies with NSAIDS suggest benefit. The addition of rofecoxib to finasteride-alone treatment has been shown to shorten the time to symptomatic improvement in IPSS and peak flow rates and adding tenoxicam to treatment with alpha-blockade also showed improvements in those same parameters compared with alpha-blockade alone [36, 37]. A meta-analysis of three randomized controlled trials showed that NSAIDS, when given over periods of 4–24 weeks, improved symptoms by 2.9 IPSS points and flow by 0.89 ml/s [38].

CRP

C-reactive protein is an acute-phase protein of hepatic origin that is associated with a wide variety of inflammatory processes in the body and is commonly used as a marker for systemic inflammation. CRP was shown to be strongly predictive of residual LUTS in men after medical treatment of prostate symptoms, independently of prostate size or other identifiable parameters [39]. Observational studies have shown a higher prevalence of LUTS in the general population to be predicted by elevated CRP values and the Olmstead County data found that men with higher CRP were more likely to develop worsening LUTS and flow rate [40, 41].

Interestingly, when women as well as men are studied, an overlapping risk of increased IPSS score with higher CRP is still seen. [42] While the patterns of voiding complaint varied in men vs women, systemic inflammation as measured by CRP may impact the voiding experience in a non-organ-specific way. Recent work has further expanded these findings to the pediatric population, where daytime voiding scores are worse in parallel with higher CRP values in girls. [43]

The persistent association of higher CRP levels with impaired voiding, and the suggestion that it operates independently of obstruction, make this marker an attractive target for continued investigation.

PDE-5i

PDE-5 inhibitors may attenuate inflammation in various disease states including inflammatory bowel disease, pulmonary hypertension, reactive airway disease, and multiple sclerosis [44]. Inhibition of type 5 phosphodiesterase (PDE-5) leads to increases in cyclic GMP (cGMP), smooth muscle relaxation and increased organ oxygenation and perfusion. PDE5 has been shown to be upregulated in rat BPH models as well as human prostate tissue [45]. Furthermore, immunohistochemistry showed prominent localization of PDE5 in prostatic vasculature [46]. It also appears to exert some anti-inflammatory effects on cultured human myofibroblast BPH cells in an in vitro model [47]. In another experimental study in a rabbit model, PDE5i reduced prostate inflammation, fibrosis, and hypo-oxygenation [48]. Additionally, daily dosing of tadalafil was shown to both prevent de novo, and reverse established prostatic inflammation in two different murine models of non-bacterial prostatitis, and also appears to have therapeutic effect in chronic pelvic pain [49, 50•].

Administration of once daily tadalafil has been shown to lead to improvement in LUTS in men when compared with placebo [51]. Based upon this, tadalafil is used for the treatment of LUTS/BPH in the USA and European Union. A recent meta-analysis of 11 randomized controlled trials found that patients receiving combination therapy with α-blockers and PDE5-i had slightly greater improvement in IPSS and maximum urinary flow rate compared with those with α-blockers alone (IPSS: MD: 1.66 CI −3.03 to −0.29) [52]. PDE-5 inhibitors are a useful therapeutic tool in LUTS, and may turn out to be a mediator of prostatic inflammation. However, whether the mechanism of this improvement in voiding in humans involves direct impact on inflammatory processes remains to be shown.

Hormones

A number of lines of evidence implicate intact hormonal signaling as important to maintenance of prostatic tissue. Male aging is associated progressively with a decrease in testosterone levels, and testosterone itself has been observed to function as a direct anti-inflammatory mediator in certain settings [53, 54]. Anti-inflammatory effect has been proposed directly in the prostate as well, where DHT has been found to be associated with the abrogation of inflammation [55, 56]. The clinical impact of this biochemical effect is unclear, and more clarity remains to be gained as the presence of DHT also contributes meaningfully to BPH progression. Testosterone in men has been suggested to function broadly as a moderating influence on inflammatory pathways [57].

Obesity is associated with prostate size and inflammation, and this appears to function at least partly via disruptions in the hormonal balance of the individual to favor estrogenic influences and decrease androgenic, as well as enhanced epigenetic inactivation of the SRD5A2 gene promoter [58•, 59]. A secondary analysis of the REDUCE trial showed that obesity enhanced prostate volume growth and attenuated

reduction by dutasteride as measured by serial transrectal ultrasounds [60].

Other groups have implicated features of hormonal signaling in the inflammation and symptomatic pathway, suggesting estrogen receptor-beta activation as preventative of inflammation, and disruptions in androgen receptor (AR) signaling as causative [61, 62]. Murine models of estrogen overabundance show significantly elevated inflammation during development, along with decreased prostatic growth [63]. More recently, the importance of intracrine androgen conversion and signaling to wild type as well as pathological cell function has come into light [64]. A separate pathway of intracrine androgen conversion exists that directly converts DHEA directly to DHT without passing through T; the impact of this pathway and others like it on the pathogenesis of BPH is understudied. An intriguing correlate of this intracrine pathway is the new understanding that immune cells, as seen in prostatic inflammation, are active participants in the hormonal milieu—not only are they reacting to circulating androgen and estrogen but also these immune cells themselves are actively synthesizing and metabolizing androgens, estrogens, and other hormones and precursors [65].

Metabolic Stress

One contributing factor in BPH/LUTS has been theorized to be the pro-inflammatory state of metabolic syndrome (MetS). MetS is a cluster of medical conditions including abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, elevated fasting glucose and hypertension. Much research has addressed the association of this constellation of disease processes with LUTS, with large meta-analyses suggesting no clear relationship although certain factors have remained associated [66••, 67].

However, MetS does have a relationship to inflammation and subsets within that disease state may be important in direct or indirect ways. In vitro studies of human BPH cells stimulated with LDL have shown enhanced production of pro-inflammatory cytokines. This correlates with the histopathology of BPH specimens which show an inflammatory score increases as a function of MetS components [68]. A meta-analysis by Gacci and colleagues showed that patients with MetS have higher although unimpressively different total prostate volume vs those without MetS (+ 1.8 mL, 95% CI 0.74–2.87; $P < 0.001$) [69]. As noted above, the pro-inflammatory state associated with central obesity may be associated with the inactivation of the SRD5AR-2 gene promoter, leading to accelerated BPH progression.

One series of men selected for radical prostatectomy found those with MetS had higher periurethral fibrosis and higher IPSS scores (12 vs 8, $p < 0.05$) despite same-sized prostates at removal. Interestingly, those with MetS and higher scores also had significantly higher measures of obstruction on urodynamic testing, leaving open the question of whether mismatching of morphological obstruction such as a median lobe or similar anatomic defects may have contributed to the inflammation [21].

Diabetes, and specifically hyperglycemia, appears to mediate a direct bladder dysfunction in murine models that results in urinary frequency, increased post-void residual and decreased voided volume. The degree to which this effect is manifested in the prostate, and that element of further contribution to human voiding dysfunction aside from what is mediated through bladder damage, is unclear [70].

Neuronal Cross Talk

For BPH associated LUTS to occur, the prostate must exert an effect on the bladder. There has been increasing evidence of a complex neuronal interaction between the two by which this effect is mediated. Several rat models have shown a high proportion of dichotomized afferent nerves from the bladder and prostate providing a neuronal anatomical pathway by which voiding dysfunction could be mediated [71, 72]. Funahashi and colleagues further illustrated that inducing non-bacterial prostatic inflammation in rats led to bladder hyperexcitability and an increase in non-voiding contractions and urinary frequency [71]. This suggests a mechanism for how loco-regional inflammation within the prostate could worsen LUTS in men.

Summary

In which men are LUTS acquired as a direct or indirect consequence of prostatic inflammation? Who is impacted by systemic inflammation? What are the relationships between these processes and the development of prostate enlargement with or without obstruction?

When the data are examined at a clinically relevant level, two points become apparent. First, inflammation is common in the prostate. Definitions and prevalence vary from 45 to 100%, but undoubtedly it is a common process in this organ.

Secondly, the clinically significant impact of in-gland inflammation, broadly termed, is variable and difficult to define. As a process, inflammation is associated with a large number of cytokines and growth factors which can lead to fibrosis. It may be that there are subsets of inflammation that are more associated with the development of LUTS or the growth of the gland itself; for example, different markers of inflammation had differing relationships to different outcomes in one study, and location of inflammation seems clearly to impact the ease with which it is detectable and potentially the impact [10].

Symptoms A clinically significant IPSS change of greater than 3 is necessary to reach the threshold of perceptibility and while large groups of well-studied patients do show a statistically significant increase in IPSS score in the presence of inflammation in prostate biopsy tissue, it is so small as to be nearly negligible [20]. It is quite unlikely that patients in the placebo arm of the REDUCE trial would notice the increases of 0.4 IPSS points (8.2 vs 8.8) or the 0.2-point change in the irritative subset of symptoms (4.1 vs 4.3) and the statistical significance comes as a result of powering that identifies clinically trivial differences.

Hyperplasia The differences in prostate size with and without inflammation are statistically significant in the REDUCE and MTOPS datasets, again working with tissue from needle biopsy, but the increases of 3.1 g and 4.3 g, respectively, with inflammation are small and difficult to attribute clinical significance to. In the lone autopsy series mentioned above, inflammation was more common in glands with BPH, and was usually found within those nodules, but was not more common in larger than smaller prostates.

Acute Urinary Retention Inflammation appears to be associated with an increased risk of AUR, roughly doubling the chance of this event when compared with the non-inflamed prostate. Since the occurrence of urinary retention in men is associated with increased morbidity and mortality, deeper understanding of this relationship is desirable—whether it occurs through direct and avoidable causation, or shared underlying processes.

Aside from the association with AUR, the clinically significant impact of inflammation on BPH progression, and voiding, has been fairly hard to define when viewed across broad groups. It seems likely that better understanding of the distinct mechanisms in certain subsets of inflammation, hyperplasia, and symptomatology may allow definition and delineation of phenotypic groups, with differing etiologies and risks, within the broad umbrella of BPH/LUTS. Prostatic inflammation may simply reflect an increased risk of the enlarged and nodular prostate to become irritated, whether due to inspissated secretions, ischemia, autoimmune response, or the indirect effect of systemic inflammation; alternatively, it may play a key role in a yet-to-be defined subset of men with BPH and LUTS.

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Compliance with Ethical Standards

Conflict of Interest Granville L. Lloyd, Jeffrey M. Marks, and William A. Ricke each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
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- •• Of major importance

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transition zone biopsy cores were analyzed and compared with their prospectively collected clinical variables. CD-4 was associated with BPH progression as defined by IPSS progression of 4 points (HR = 1.86 (1.16, 2.98)). CD-4, CD-8, and CD-68 was associated with an increased risk of developing acute urinary retention.

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