Inflammatory Mechanisms Associated With Prostatic Inflammation and Lower Urinary Tract Symptoms

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Inflammation is a common finding in histologic prostate specimens obtained from aging men. Accumulating data suggest that inflammation may play an important role in the development of benign prostatic hyperplasia (BPH), and the development and progression of lower urinary tract symptoms (LUTS). Inflammatory processes may contribute to prostatic enlargement directly through stimulation of prostate growth, or, alternatively, through decreasing prostatic apoptosis. Inflammatory processes may also impact other components of the urogenital tract, such as the bladder, and contribute to LUTS regardless of the presence of prostate enlargement. Therefore, current research offers clues about converging inflammatory pathways that may be targeted to improve treatment of BPH and/or LUTS, as well as identifying potential targets for the prevention of these syndromes.

Introduction

Prostate growth and enlargement and clinically significant lower urinary tract symptoms (LUTS) are extremely common in aging men. Benign prostatic hyperplasia (BPH) is evident in 50% of men 51–60 years old [1], while almost half of all men develop clinically significant LUTS as they age [2]. In 2000, medical visits, treatments, and hospitalizations for BPH alone cost about $1.1 billion, stemming from 87,000 hospitalizations and 4.4 million outpatient visits. Outpatient pharmacotherapy (primarily directed toward ameliorating LUTS) was estimated to cost $194 million annually between 1996 and 1998 [3]. As the population ages, the number of men affected by these conditions will rise dramatically, with more than 11 million men expected to meet American Health Care Policy and Research guidelines for discussing BPH treatment options by 2030 [4]. Therefore, BPH and LUTS have a major impact on public health and medical care expenditures. However, despite the ubiquity of these syndromes among aging men, little is known about the factors that lead to their development or exacerbation. Identification of biologic pathways that contribute to the development and progression of BPH and LUTS would substantially contribute to identifying strategies for improved treatment and prevention. This could significantly improve the quality of life of affected men and result in a substantial reduction in related health care costs.

Prostate enlargement may cause prostatic compression of the urethra, subsequently leading to LUTS, although correlations between prostatic enlargement and LUTS severity are relatively modest. LUTS may also develop in the absence of prostate enlargement, suggesting that multiple factors contribute to the development of prostatic enlargement and LUTS. However, an emerging body of evidence suggests that inflammatory processes may play important roles in the development of these syndromes. This review focuses on literature examining the possible role of inflammation in the development of prostatic enlargement and LUTS, the potential role of inflammation in prostate growth and bladder dysfunction, and how therapies for BPH and LUTS may target points in inflammatory pathways.

Evidence for the Role of Inflammation in Prostate Growth and LUTS

Chronic and acute inflammation have been frequently noted in prostate biopsy sections and in tissue obtained during prostatic resection for treatment of BPH [5–8]. However, although inflammation is an extremely common observation (range, 43%–98%) in prostatic biospecimens, it is difficult to determine whether inflammation is a normal biologic part of the aging process or if it actually contributes to prostatic enlargement, LUTS development, and/or the development of acute urinary retention (AUR).

Clinically, several cross-sectional studies have suggested associations between the presence of inflammatory infiltrates and increased prostate volume. In a retrospec-

tive review of tissue specimens obtained from prostatic resection for treatment of BPH, Di Silverio et al. [6] found that the presence of chronic inflammation increased as prostate volume increased, from 8.9% in prostates 30–39 mL to 61.4% in prostates 80–89 mL. In a prospective, longitudinal study, 2.6% of men participating in the Medical Therapy of Prostate Symptoms (MTOPS) trial had acute inflammation and 43% had chronic inflammation in prostatic biopsy specimens at baseline. Those with acute inflammation also had significantly larger prostate volumes (41.1 mL vs 36.8 mL) [9••].

Clinical studies examining associations between markers of inflammation in LUTS development have shown much weaker associations than those observed between prostatic inflammation and prostate volume. However, the presence of elevated C-reactive protein, a nonspecific marker of inflammation, was associated with a nonsignificant increased likelihood of LUTS in men participating in the Third National Health and Nutrition Examination Survey [10••]. Minor correlations were also observed between the presence of prostatic inflammation and LUTS in men participating in the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial [11•]. Roehrborn et al. [9••] also found that MTOPS participants with acute inflammation in their biopsy specimens were slightly more likely to develop worsening LUTS compared with those without acute inflammation. These minor correlations between prostatic inflammation and the presence of LUTS are perhaps unsurprising given the relatively modest correlations that have been observed between prostate volume and LUTS [12,13].

Finally, several studies have found moderate to strong associations between the presence of prostatic inflammation and AUR. In cross-sectional studies, patients with AUR referred to urology clinics were more likely to have evidence of inflammation in prostatic specimens compared with men referred for benign prostatic obstruction [14•,15•]. Intraprostatic inflammation was also present in 70% of men requiring transurethral prostatic resection for AUR compared with 45% of men requiring resection to treat LUTS [16•]. Additionally, Roehrborn et al. [9••] found that patients with acute inflammation in baseline prostate biopsies were more likely (2.4% vs 0.6%) to develop AUR compared with those without such findings [9••]. Taken together, these studies suggest that inflammatory processes may contribute to the development and/or exacerbation of BPH and LUTS.

Inflammation and Prostate Growth

As described above, several clinical studies have found associations between inflammatory infiltrates in prostate biopsy sections and increased prostate volume [6,9••]. Additionally, in an animal model, administration of an immunostimulator to Wistar rats resulted in prostatic epithelial proliferation [17]. Together with the common finding of inflammatory infiltrates in prostate biospecimens, it has been hypothesized that inflammation may directly contribute to prostate growth.

The inflammatory infiltrates in prostate tissue have been primarily found to be upregulated macrophages and T lymphocytes [18,19]. Anim et al. [20] suggested that initial prostate insults are followed by macrophage responses and subsequent recruitment of T lymphocytes to the prostate tissue. Other investigators have suggested that BPH might have an autoimmune component, whereby antigenic stimuli may result in the development of a chronic inflammatory response within the prostate that leads to tissue rebuilding and stromal growth in the prostate [18,21••]. Whatever the initial trigger of inflammation, proinflammatory cytokines likely play an essential role in attracting and maintaining proinflammatory cells in the prostate tissue. Handisurya et al. [22] found that interleukin (IL) 15 was substantially increased in BPH specimens and may play an important role in attracting T lymphocytes to prostatic tissue and in stimulating their proliferation. Additionally, macrophage inhibitory cytokine-1 (MIC-1), which inhibits macrophage activity, showed downregulated gene expression in BPH tissue samples [23]. Lower MIC-1 transcription levels have also been associated with increased inflammation in BPH tissue samples [24]. Together, these studies suggest that increased attraction of macrophages and T lymphocytes to prostate tissue, and increased macrophage activity, may be important components in generating and sustaining prostatic inflammation (Fig. 1).

The mechanisms by which inflammation may lead to prostatic growth have not been elucidated; however, once activated lymphocytes and macrophages are attracted to prostatic tissue, they may secrete proinflammatory cytokines that may directly contribute to prostate growth. Steiner et al. [25] found that IL-17 mRNA and protein levels were increased in 79% of BPH tissue specimens compared with virtually no increase in prostate specimens obtained from young men. Stimulation of a BPH stromal cell culture with IL-17 also caused a substantial upregulation of the IL-6 and IL-8 cytokines [25]. These results are consistent with studies by other investigators who observed increases in IL-6 and IL-8 in seminal plasma among men with BPH compared with controls [26•]; an increased level of IL-6 was also seen in BPH epithelium compared with the epithelia and stroma of prostates obtained from controls [27]. Interferon gamma (IFN-γ), IL-2, and IL-4 have also been shown to be upregulated in BPH tissue cell lines compared with prostatic stromal cells from controls [28]. These results were supported by Steiner et al. [29], who also found upregulation of IFN-γ, IL-2, and IL-13 in BPH specimens with inflammatory infiltrates [29]. Unfortunately, most of these studies used control specimens from young (< 40 years old), healthy men, so it is unclear whether elevations in these proinflammatory cytokines are a normal component of aging,

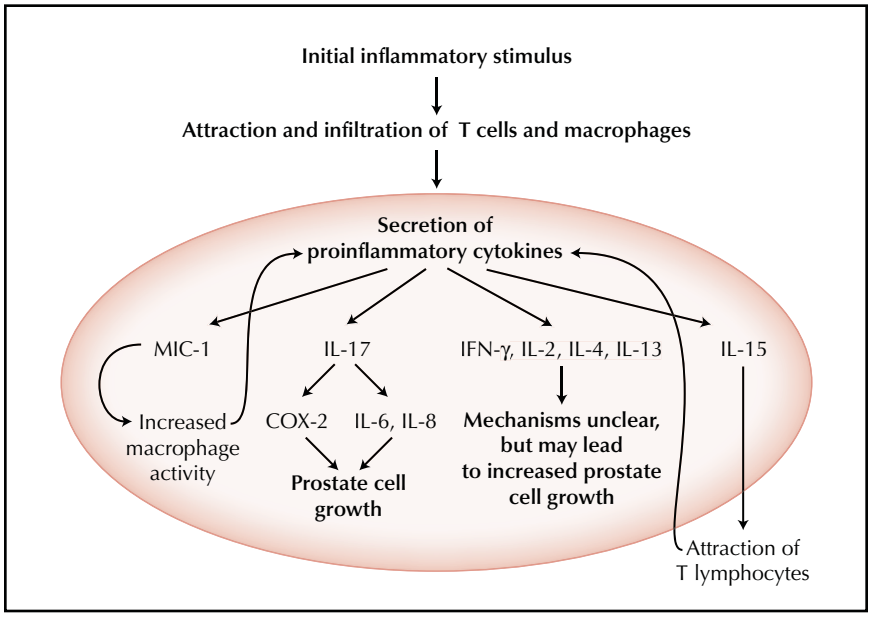

Figure 1. Possible mechanisms by which inflammatory stimuli may contribute to prostatic growth. Increased attraction of macrophages and T lymphocytes to prostate tissue, and increased macrophage activity, may be important components in generating and sustaining prostatic inflammation. COX-2—cyclooxygenase-2; IFN—interferon; IL—interleukin; MIC-1—macrophage inhibitory cytokine-1.

due to an antigenic stimulus, or the result of a chronic inflammatory process.

However, additional studies have indicated that IL-8 in particular can induce fibroblast growth factor 2 production in prostate stromal cells [30], and thereby cause prostate growth. In accordance with this observation, higher IL-8 levels have also been correlated with increased prostate volume [31]. Additionally, Kramer et al. [28] found that BPH stromal cells were upregulated by IFN-γ. Taken together, these data suggest that proinflammatory processes could stimulate the production of specific cytokines that could directly increase the growth and development of prostate stroma (Fig. 1).

Proinflammatory cytokines can also induce additional inflammatory mediators that may contribute to prostate growth. For example, IL-17 can exert a direct influence on cyclooxygenase-2 (COX-2; the enzyme responsible for converting arachidonic acid to prostaglandin) expression through stabilizing COX-2 mRNA and preventing degradation [32]. This stabilization may then result in the presence of higher levels of COX-2 and increased activity of this enzyme. In support of this hypothesis, Wang et al. [33] found that expression of COX-2 was highest in BPH tissues that also had moderate to severe T lymphocyte and macrophage infiltration. COX-2 is a known mediator of cellular growth, and measures of prostatic epithelial cellular proliferation have been found to be highest in areas with high levels of COX-2 expression [33].

It also appears that COX-2 expression may be induced by inflammation-independent pathways. Lin et al. [34••] found that the α-adrenergic pathways may also be involved in upregulation of COX-2. Stimulation of α-adrenergic receptors in BPH tissue cultures resulted in an almost 14-fold increase in COX-2 gene expression. Given these data, COX-2 may represent a convergent mediator of prostate growth in the inflammatory and α-adrenergic pathways.

Decreased apoptosis and upregulation of anti-apoptotic factors has also been observed in BPH tissue specimens. High COX-2 levels have been associated with upregulation of the anti-apoptotic gene BCL-2, and overexpression of BCL-2 in BPH epithelial cells has also been noted [33,35]. Gerstenbluth et al. [7] also found intensified BCL-2 staining in 10 BPH tissue specimens that had evidence of chronic inflammatory infiltrates. Shariat et al. [36•] found high levels of survivin, a member of the apoptosis gene family that promotes cellular survival, in BPH stroma compared with normal prostate cells. These investigators also found that higher levels of survivin expression were correlated with higher LUTS, decreased maximum urinary flow rates, and increased postvoid residual volumes [36•].

These data suggest that inflammatory mediators may contribute to prostatic epithelial and stromal cell growth both directly, through growth induction via cytokines that stimulate production of prostatic growth factors (Fig. 1), and indirectly through decreases in prostate cell death via downregulation of prostate cell apoptosis.

Potential Anti-Inflammatory Mechanisms of Treatments for BPH

The mechanisms of several common treatments for BPH may exert positive effects at various points in the pathways linked to inflammation in addition to their commonly accepted mechanisms of action (Table 1). For example, finasteride inhibits the conversion of testosterone to dihydrotestosterone, but has also been shown to increase apoptosis in prostatic tissue [37], presumably through downregulation of BCL-2 [38]. Some α1-adrenergic receptor inhibitors (doxazosin, in particular) have also been shown to cause apoptosis in prostate cells [39,40]. In the intact human, Roehrborn [41•] did not find a reduc-

Table 1. Possible mechanisms by which therapies may improve BPH and/or LUTS by interrupting inflammatory processes

Study	Drug type	Mechanism of action	Result
Rittmaster et al. [37], Huynh [38]	Finasteride	Downregulation of BCL-2	Increased apoptosis of prostate cells
Tahmatzopoulos and Kyprianou [39], Garrison and Kyprianou [40], Partin et al. [59]	α-adrenergic receptor inhibitors	Decreased function of α-adrenergic pathways	Increased apoptosis of prostate cells
St. Sauver et al. [42••], Minnery et al [43•], Takagi-Matsumoto et al. [50], Angelico et al. [51•], Erdogru et al. [52], Cardozo and Stanton [54], Cardozo et al. [55], Araki et al. [56], Di Silverio et al. [57••]	Nonsteroidal anti-inflammatory drugs	Decreased COX-2 activity or unknown mechanisms	Decreased prostate volume; increased apoptosis of prostate cells; i ncreased bladder capacity; restoration of urothelial cell-cell interactions; improved LUTS
Vela Navarrete et al. [44]	*Serenoa repens* (saw palmetto)	Unknown	Decreased inflammatory infiltrates in the prostate

BPH—benign prostatic hyperplasia; COX-2—cyclooxygenase-2; LUTS—lower urinary tract symptoms.

tion in prostate size among men treated for 3 months with alfuzosin, but did not rule out the possibility that longer-term treatment might impact prostate size or that apoptosis might not be a feature of alfuzosin.

Use of anti-inflammatory medications in treating BPH has not been widely studied; however, in a group of men residing in Olmsted County, our group found that men who took a nonsteroidal anti-inflammatory drug (NSAID) were about twofold less likely to develop an increased prostate volume compared with those who did not [42••]. Minnery and Getzenberg [43•] also found that ibuprofen could reduce cell viability and induce apoptosis in a BPH cell line.

Finally, Vela Navarrete et al. [44] found that patients taking a common phytotherapy for BPH (Permixon [BioMedic, Miami, FL], a sterol lipid extract of Serenoa repens [saw palmetto]), had fewer inflammatory infiltrates in resected prostate specimens, suggesting that this agent may have anti-inflammatory properties.

These data suggest that several drugs may reduce prostate volume by acting at various points in the inflammatory pathway, possibly through direct action on the anti-apoptotic protein BCL-2, indirectly through the COX-2 pathway, or through as yet unidentified mechanisms.

Inflammation and the Bladder

As the development and progression of LUTS cannot be completely attributed to prostatic growth, it is likely that LUTS may also occur due to changes in other components of the male urologic system. The bladder is an obvious component that may contribute to LUTS. Bladder outlet obstruction due to prostatic enlargement or increased smooth muscle tone of the prostate may result in bladder wall thickening and eventual loss of optimal bladder function. However, changes in the bladder may occur apart from prostatic enlargement and may contribute to the LUTS experienced by many aging men. While associations between inflammation and bladder changes have not been examined in as much detail as inflammation and the prostate, a number of studies suggest that inflammation may also play a role in bladder changes and subsequent development of LUTS.

Prostaglandins mediate contractions of animal and human bladder cells [45,46]. Although the methods by which prostaglandins may mediate symptoms of urinary urgency are still unclear, cyclooxygenases synthesize prostaglandins from arachidonic acid, suggesting an important role for COX-related pathways in bladder-related pathologies.

Increased prostaglandin production may occur due to mechanical factors rather than infectious, environmental, or autoimmune stimuli. Park et al. [47] found that mechanical stretching of bladder smooth muscle cells, secondary to bladder outlet obstruction in female mice, results in a substantial upregulation of COX-2 and a subsequent increase in prostaglandin E2 (PGE2) levels. In addition, bladder smooth muscle cell proliferation was observed following cell stretching, and this response could be inhibited by addition of a COX-2 inhibitor, suggesting that COX-2 may participate in bladder wall thickening via increased bladder cell growth. Therefore, bladder outlet obstruction due to prostatic enlargement or increased adrenergic function could stimulate the COX-2 pathway in the bladder, resulting in increased prostaglandin synthesis and increased LUTS.

Additionally, while bladder muscle cells contract in response to prostaglandins, human detrusor smooth muscle cells also can produce a number of proinflammatory

cytokines. Upon stimulation with the proinflammatory mediators IL-1β and tumor necrosis factor, detrusor cells cultured from bladder biopsies were shown to upregulate monocyte chemoattractant protein 1 (MCP-1), IL-6, IL-8, and chemokine (C-C motif) ligand 5 [48,49•]. Activated bladder muscle cells may therefore directly contribute to bladder inflammation by recruiting inflammatory cells to the bladder milieu. Further studies are necessary to determine whether bladder inflammation may contribute to LUTS via COX-2 dependent pathways, independent inflammatory pathways, or both.

Effect of Anti-Inflammatory Treatments on Bladder Function

Given the role of COX-2 and prostaglandins in bladder function, a number of investigators have examined the effects of NSAIDs on bladder function. Specific NSAIDs have been shown to increase bladder capacity in normal rats, and to reduce micturition frequency in rat models of cystitis [50]. More potent COX-2 inhibitors appear to be more effective at increasing bladder volume capacity in rat models of micturition [51•]. Selective COX-2 inhibitors are also able to restore urothelial cell-to-cell interactions that were damaged in rat models of partial bladder outlet obstruction [52]. However, Meini et al. [53] found that the contractile response of the rat bladder in a model of persistent inflammation was not improved after treatment with COX inhibitors, suggesting that chronic inflammation may change the ability of the bladder to respond to prostaglandin stimuli. If this is the case, men with long-term bladder inflammation may not respond well to NSAID treatments.

Few studies have examined the use of NSAIDs in directly treating LUTS; however, two small trials by Cardozo et al. [54,55] indicated that flurbiprofen and indomethacin could substantially decrease frequency, urgency, and urge incontinence in women with detrusor instability compared with placebo. In another study, loxoprofen sodium use once a day improved nocturia symptoms in 74% of patients with BPH [56], and total urinary symptoms improved in men with BPH who were treated with rofecoxib and finasteride compared with finasteride alone. These positive effects beyond that of finasteride were limited to an initial short-term interval (4 weeks), as, by 24 weeks, both groups showed similar improvements [57••]. Additionally, in support of a positive role for NSAIDs in preventing development of LUTS, we found that men who took a daily NSAID were less likely to develop moderate to severe LUTS [42••].

These data suggest a promising role for NSAIDs in the treatment (and possibly prevention) of LUTS. However, NSAID use may not be completely benign in terms of improving LUTS because the adverse gastrointestinal effects of NSAIDS are well known. Additionally, Verhamme et al. [58••] reported that men who were currently taking an NSAID were at increased odds of developing AUR, with the highest risk observed among men who had recently begun use of the agent. The authors postulate that in some men, reducing prostaglandin synthesis in the bladder could prevent the bladder from emptying and trigger acute urinary retention. Given the nonspecific effects of NSAIDs, further studies are clearly necessary to determine whether this class of drugs may be useful in the treatment and/or prevention of LUTS.

Conclusions

Accumulating evidence suggests that inflammatory processes affecting the prostate and bladder may play essential roles in the development and maintenance of prostate growth and LUTS. While the inflammatory triggers and precise mechanisms by which prostate growth and LUTS may develop are still unclear, current research offers clues about converging pathways that may be targeted to improve treatment and identify potential targets for prevention of these conditions.

Disclosures

Dr. Sauver reported no potential conflicts of interest relevant to this article. Dr. Jacobsen is an unpaid consultant for Merck.

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