Articles in PresS. Am J Physiol Renal Physiol (July 20, 2016). doi:10.1152/ajprenal.00602.2015

THE ROLE OF PROSTATE INFLAMMATION AND FIBROSIS IN LOWER URINARY TRACT SYMPTOMS

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Abstract

Lower urinary tract symptoms (LUTS) in aging men are extremely common. They have historically been attributed to benign prostatic hyperplasia (BPH), enlargement of the prostate and bladder outlet obstruction. However, recent studies have revealed acute and chronic inflammation to by highly associated with LUTS, correlated with prostatic enlargement and implicated prostate fibrosis as a contributing cause of bladder outlet obstruction. This review examines the evidence implicating inflammation and fibrosis in BPH/LUTS. It identifies potential mechanisms by which inflammation may drive nociceptive signaling as well as hyperplastic growth and fibrosis and identifies targets for pharmacologic intervention. This is a promising area for research and development of novel therapies to prevent or more effectively treat LUTS in aging men.

Background: Lower urinary tract symptoms (LUTS) are common in aging men and include obstructive symptoms such as weak urinary stream, straining to void, and a sense of incomplete emptying as well as irritative symptoms such as frequency, urgency, nocturia. These symptoms have generally been attributed to prostatic enlargement and an increase in outlet resistance with secondary effects on bladder function. Benign prostatic hyperplasia (BPH) is an age-related, androgen-dependent progressive enlargement of the prostate gland resulting from a non-malignant proliferative process that includes both epithelial and stromal elements. A contribution of prostatic enlargement to development of LUTS is unequivocal. However, recent studies have shown that development of LUTS is multi-factorial. Changes in smooth muscle tone in the prostate and bladder neck may increase outlet resistance independent of significant enlargement (Nickel, 1999). Age-related decrease in detrusor contractility and primary detrusor over-activity contribute significantly to lower urinary tract symptoms. Recently, prostatic inflammation has been found to be associated with prostatic enlargement, severity of LUTS and symptomatic progression. That is the focus of this review.

Prostate inflammation: Prostatic inflammation is evident by inflammatory cells infiltrating the prostatic stroma, epithelium, and/or prostate glands (Cotran RS et al, 1999; Nickel et al., 2008). Acute and chronic inflammation has been identified in 40-50% of prostatic samples obtained by biopsy, surgery, or autopsy (Delongchamps et al., 2008; Kohnen and Drach, 1979; Theyer et al., 1992; Steiner et al., 1994; Kramer et al., 2006; Di Silverio, et al., 2003). Chronic inflammation is more common than acute inflammation (78% versus 15%, respectively; Moreira et al., 2014).The etiology of prostatic inflammation is likely multi-factorial. Urine refluxes freely into the prostatic ducts (Kirby, 1982) and provides a route for bacterial colonization. (Weiss, 1983; Krieger and Riley, 2002). Other potential causes include viruses, dietary components, changes in serum testosterone and estrogen levels, autoimmune mechanisms, and reflux of noxious chemicals in the urine (DeMarzo et al., 2007; Gandaglia et al., 2013). In addition, prostate inflammation can be triggered by metabolic alterations including metabolic syndrome and dyslipidemia (Vignozzi et al 2016; DeNunzio et al 2012; Freeman

and Solomon 2011). All told, these studies point to a systemic and metabolic cause for prostatic inflammation.

Inflammation is more common in men with BPH/LUTS and correlates with symptom severity and risk for progression. In a prospective study of autopsy specimens obtained from 93 men with histological evidence of BPH, chronic inflammation was found (primarily in the transitional zone) in 75% of prostates examined compared to 55% of prostates not affected by BPH (Delongchamps 2008). Evidence of inflammation on baseline biopsy in the Medical Therapy of Prostate Symptoms (MTOPS) trial correlated with prostate volume (41 vs 37 cc; p=0.0002) and greater risk for symptomatic progression, urinary retention and need for surgery (Roehrborn, 2006). It has been postulated that inflammation may contribute to prostate enlargement by inducing hyperplasia. However, it has also been postulated that prostatic inflammation could cause urinary frequency and urgency by directly influencing bladder sensation and detrusor function (Geppetti, 2008). Pelvic organs share innervation and it has been shown that inflammation of one pelvic organ can produce cross-sensitization of other pelvic viscera (Qin, 2005; Rudick, 2007; Ustinova, 2007; Ustinova, 2006). This has been postulated to occur, in part, by triggering activation of afferent sensory nerves (Candenas, 2005; Lecci, 2001; Maggi, 1997). Recently we showed that isolated prostate inflammation in the laboratory mouse produces a significant increase in voiding frequency (Lee et al., 2015). The anatomic basis for this may be convergent innvervation of the bladder and prostate: afferent neurons in the lumbosacral dorsal root ganglia providing afferent innervation of the both the prostate and bladder (manuscript submitted). These observations resonate with the selective correlation of inflammation with irritative LUTS in the REDUCE trial (Nickel et al., 2008).

Prostatic fibrosis and bladder outlet obstruction: While prostatic enlargement correlates with increased urethral resistance and LUTS (Bushman, 2009), many men experience bladder outlet obstruction and symptoms in the absence of significant prostatic enlargement (Blaivas, 1996;

Bushman, 2009). Increased adrenergic tone of smooth muscle in the prostate may be a contributing factor, but the frequent ineffectiveness of medical therapy with alpha-blockers argues for additional mechanisms. It has been speculated that fibrosis of the prostate may increase urethral restance and several studies have provided evidence for periurethral firbrosis,. decreased elastin and changes in tissue compliance (Bercovich et al., 1999; Diavan et al. 1999; Morrison et al., 2000; Ma et al., 2012; Rodriguez-Nieves and Macoska 2013; Cantiello et al. 2013; Bauman et al. (2014). The etiology of prostate fibrosis is uncertain but chronic inflammation is an obvious candidate. Studies in the mouse have shown that prostate inflammation does induce an increase in collagen content (Wong et al., 2014a) and there is a suggestion in human studies of a correlation between inflammation and fibrosis (Cantiello et al., 2013).

Cells and mechanisms. The majority of infiltrating leukocytes in the inflamed human prostate are chronically-activated T lymphocytes and macrophages (Theyer et al. 1992; Steiner et al. 2003). Mouse models of inflammation exhibit very similar infiltrative components as inflamed human prostates (Boehm et al 2012; Haverkamp et al 2011). Th1 cells regulate the immune response to intracellular pathogens via IFN and IL-2. Th2 cells produce IL-4, IL-13 and IL-5 and regulate the hypersensitivity response. Th17 cells are responsible for host defense against extracellular pathogens (Rautajoki et al. 2008) through IL-17 and IL-21. Resident epithelial and stromal cells express several toll-like receptors including TLR-4, TLR-5, TLR-7 and TLR-9, and also produce IL-1, IL-6, and IL-15 during inflammation (Kramer & Marberger 2006). Prostatic epithelial cells express class II MHC molecules that participate in organ-specific inflammation (Penna et al. 2009), resulting in the production of IL-6, IL-8 and CXCL10 and leukocyte recruitment (Penna et al. 2009). Stromal cells express CD80, CD86, CD40, and CD134L (Penna et al.2009) and activate T lymphocytes directly. These activities contribute to a chronic state of inflammation.

The cytokines and growth factors highly expressed in BPH include IL-1, IL-6, IL-8, IL-15, IL-17, IFNγ, TGFβ, FGF2 and 7, and IGF-1 (Handisurya et al 2001; Steiner et al 2003; Hahn et al. 2014; Giri and Ittman 2001). These cytokines have been proposed as a link between chronic prostate inflammation and prostatic hyperplasia because they intersect with critical stromal and epithelial paracrine signaling pathways that regulate prostate growth. The Jak-STAT signaling pathway is induced by a number of these cytokines, most notably IL-6 and IL-1 (Shankar et al 2014; Jerde and Bushman 2009; Verma et al 2014). The NFκB signaling pathway is a major player in inflammatory signaling (Bouraoui et al 2012) and is induced by IL-1 downstream of MyD88. Interesting, androgen receptor signaling also results in activation of this pathway (Atawia et al 2014). Interesting, androgens have also been shown to play a critical role as anti-inflammatory agents, as men on anti-androgen therapy develop prostatic inflammation; this has been corroborated in mouse models (Izumi et al 2014). Phosphoinositide signaling is the major pathway downstream of IGF-1 and is highly activated in the epithelium of BPH and inflamed prostates (Hahn et al 2014). Secreted ligands of G-protein-coupled receptors (GPCRs) including prostaglandins, epinephrine, acetylcholine, histamine, and kinins activate pathways that include PKCs, cAMP, nitric oxide (NO), and phosphodiesterases (PDEs) during prostatic inflammation.

Opportunities for improving care. Recent studies of BPH/LUTS strongly suggest it to be a complex symptomatic condition with a multifactorial etiology. Improvements in diagnosis and treatment of BPH/LUTS will hinge upon finding methods to sub-classify patients according to etiology and to select the most efficacious treatment. In this regard it is notable that there is evidence suggesting that patients with high-grade prostate inflammation are less likely to respond to standard medical therapy (Kwon et al., 2010). If this is true, then non-invasive biomarkers of inflammation would be useful to identify patients likely to respond to medical therapy and at greater risk for symptomatic progression and urinary retention. Greer et al. (2015) used liquid chromatography mass spectrometry to compare over 800 proteins in BPH/LUTS patients and controls. Gene ontology (GO) analysis of the 50

differentially expressed proteins proteins showed revealed many were involved in inflammatory responses and implicated in fibrosis. Additionally, targeting the noted metabolic alterations associated with BPH-LUTS (Vignozzi et al 2016) could have the systemic effect of reducing prostatic inflammation in patients with LUTS, and therefore could have a beneficial impact on LUTS severity and progression.

Novel therapeutic targets involving inflammatory signaling. A recent comprehensive review and meta-analysis by Kahokehr and associates demonstrates that there is a therapeutic benefit to treating BPH with anti-inflammatories (Kahokehr et al 2013). Additionally, the specific COX-2 inhibitor celecoxib has been shown to reduce BPH symptomology (Falahatkar et al 2008). This provides proof-of-principle for efficacy or therapeutically targeting prostate inflammation and impels the search for therapies to target inflammatory pathways in BPH.

The new awareness of inflammation's role in BPH has led to speculation that established medical therapies for BPH may be related to secondary anti-inflammatory effects. **[Table 1.]** Alpha-adrenergic antagonists are generally considered to act by relaxing the smooth muscle of the bladder neck and prostate but could more generally block the actions of epinephrine induced during prostatic inflammation. The 5-alpha-reductase inhibitor finasteride interferes with androgen action in the prostate, but it also has anti-nociceptive and anti-inflammatory actions (Duborija-Kovacevic et al. 2008). The phosphodiesterase type-5 (PDE5) inhibitor tadalafil has been approved for treatment of BPH-LUTS. PDE5 inhibitors increase nitric oxide synthase (NOS) and NO activity, inactivate cGMP-mediated ρ-kinase, and decrease of autonomic hyperactivity in the bladder (Kang et al. 2007). However, PDE activity is induced during inflammation and part of the efficacy of PDE5 inhibitors could be due to anti-inflammatory effects. Indeed, a recent study showed PDE5 inhibitors have substantial anti-inflammatory activity in the prostate (Vignozzi et al, 2013; Peixoto et al. 2015). The role of histamine in neurogenic inflammation is well-established (Rosa and Fantozzi, 2013), and given the strong neuronal component to prostatic inflammation, it is possible that histamine antagonism may be

effective as anti-inflammatories in the prostate. Similarly, tachykinins and calcitonin gene-related peptide (CGRP) are neuropeptides present in the prostate, and are highly produced during neurogenic inflammation. Both are involved in prostatic and bladder smooth muscle contraction (Buljubasich et al.1999; Ventura et al., 2000). Similar to the sensory neuropeptides, endothelins are neurogenic inflammation-produced peptides involved in nerve-mediated contractions (Lau et al. 1999), and blockade of ET receptors circumvents inflammation-induced contraction as well as proliferation of resident cells (Saita et al. 1998)

Fibrosis as a target of prevention or treatment. Recent evidence suggesting prostatic fibrosis plays a central role in the development of bladder outlet obstruction in aging men begs the question – can fibrosis be prevented or reversed? Efforts to prevent fibrosis will depend on identifying the actual etiologies and natural history of changes in prostate collagen and elastin content. This is a fertile area for investigation. We have shown that fibrosis of the mouse prostate induced by inflammation of limited duration is partially reversible (Wong et al., 2014b), however, the reversibility of fibrosis in the human prostate has not been examined. Clearly, proving the associations of inflammation, fibrosis and bladder outlet obstruction and then development of medical or minimally invasive therapies to both prevent and reverse prostate fibrosis will be a research priority.

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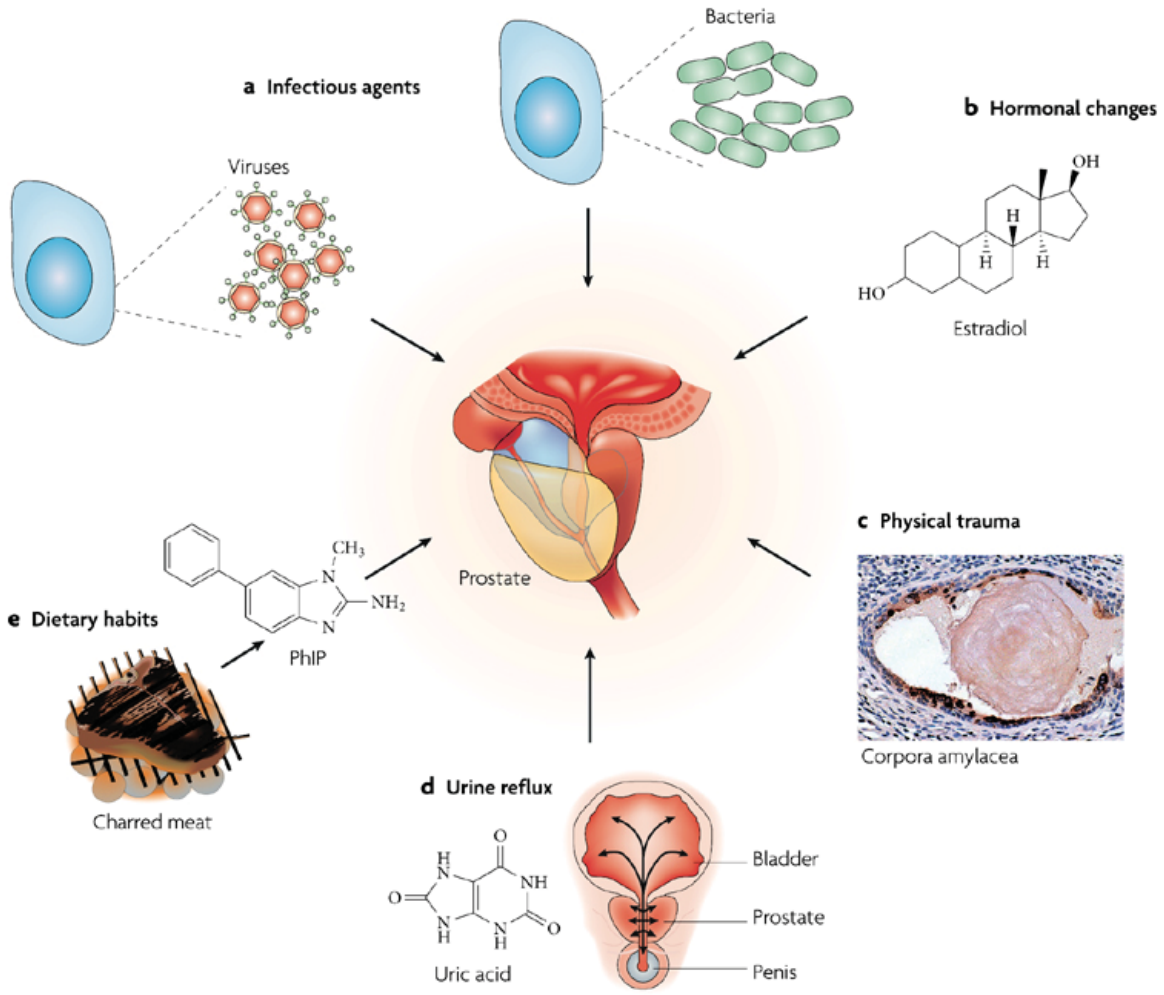
Figure 1. (DeMarzo et al. 2008) Prostatic inflammation has numerous potential causes, including infectious agents, dietary habits, hormonal changes, and physical trauma and urinary reflux.

Drug Class	Proposed Mechanism	Examples	Current Status
Alpha-adrenergic antagonists	1. Smooth muscle relaxation 2. Anti-nociceptive 3. Anti-inflammatory-uncertain mechanism	Alfuzosni Prazosin Doxazosin Tamsulosin Terazosin	Approved First Line Therapy
5-alpha reductase inhibitors	1. Blockade of DHT synthesis from T 2. Anti-inflammatory-uncertain mechanism	Finasteride Dutasteride	Approved
NSAIDs	Blockade of prostaglandin synthesis	Naproxen Ibuprofen Celecoxib	Approved, OTC Often suggested by Physician
Phosphodiesterase 5 inhibitors	Inhibition of Type 5 PDE isoform 1. Smooth muscle relaxation 2. Blockade of leukocyte infiltration	sildenafil tadalafil	Approved
Purinoceptor antagonists	Blockade of P2X1-purinoceptors		In development
Anti-histamine	Anti-inflammatory action at H1 receptors	Numerous OTC	Approved, OTC Often suggested
Endothelin antagonists	Blockade of inflammatory infiltrate at ET receptors	Ambrisentan Atrasentan Bosentan	Off label Approved for cancer
Rho Kinase inhibition	Blockade of inflammatory infiltrate by small GTPase inhibition		In development

Table 1: A summary of current pharmacological therapies for BPH targeting components of inflammation or inflammatory signaling.


a Infectious agents
Bacteria
Viruses
b Hormonal changes
OH
H
H
H
HO
Estradiol
Prostate
c Physical trauma
Corpora amylacea
e Dietary habits
CH3
N
NH2
N
PhIP
Charred meat
d Urine reflux
O
H
N
NH
O
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H
O
Uric acid
Bladder
Prostate
Penis