Published in final edited form as:

Nat Rev Urol. 2013 September ; 10(9): 546–550. doi:10.1038/nrurol.2013.149.

Prostatic fibrosis, lower urinary tract symptoms, and BPH

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Abstract

Lower urinary tract symptoms (LUTS)—constituting a spectrum disorder that encompasses weak stream, nocturia, and sensations of incomplete emptying and intermittent or hesitant urination—are indicative of lower urinary tract dysfunction (LUTD). LUTD is a progressive disease that can lead to bladder dysfunction if left untreated or treated ineffectively. Sequelae include urinary retention, recurrent UTI, bladder calculi, and, eventually, renal impairment. LUTD involving the prostate is associated with both ageing and inflammation. Tissue inflammation resulting from ageing, infection, or other inflammatory disease processes (for example, type 2 diabetes mellitus) is epidemiologically associated with the subsequent development of tissue fibrosis in multiple organ systems, including the prostate. Recent studies show that tissue fibrosis in the lower urinary tract is associated with LUTD, and suggest that fibrosis might be a previously unrecognized pathobiology that contributes to LUTD. Thus, antifibrotic therapeutic agents should be considered as a new approach to efficaciously treating men with LUTD, especially those who don't experience durable responses to 5 α -reductase inhibitors or α -adrenergic receptor antagonists.

Introduction

Lower urinary tract symptoms (LUTS) are a costly and potentially critical medical problem for millions of ageing men. This spectrum disorder encompasses symptoms such as weak stream, nocturia, and sensations of incomplete emptying and intermittent or hesitant urination, all of which are indicative of lower urinary tract dysfunction (LUTD). If left untreated or treated ineffectively, LUTD can progress to bladder dysfunction, which can lead to urinary retention, recurrent UTI, bladder calculi, and, eventually, renal impairment.^{1–5} LUTD is often, although not always, concomitant with BPH—a proliferative but nonmalignant enlargement of the prostate.

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Competing interests

The authors declare no competing interests.

Author contributions

Both authors contributed towards researching, writing, editing, discussing, and reviewing the manuscript.

Surgical ablation of prostate tissue and medical approaches to targeting androgen activity (for example, 5 α -reductase inhibitors) or smooth muscle contractility (for example, α -adrenergic receptor antagonists) can be utilized to manage LUTD. In the USA, there has been a steady decline in the use of surgical transurethral prostatectomy (TURP) over the past 10 years, as well as a steady increase in the use of minimally invasive technologies (MIST), particularly laser vaporization.^{6,7} In a recent study of 1,645 hospital patients with LUTS, the 4-year retreatment rate for laser ablation was 8.3% compared with 12.8% for TURP.⁸ A community-based study reported significant improvements in LUTS after treatment with either TURP or laser vaporization, but not with 5 α -reductase inhibitors or α -adrenergic receptor antagonists (which only stabilized LUTS).⁹

However, other studies have shown a significant improvement in LUTS in men treated with α -adrenergic receptor antagonists or 5 α -reductase inhibitors (both alone and in combination). For example, the Medical Therapy of Prostatic Symptoms (MTOPS) study showed that monotherapy with either doxazosin (an α -adrenergic receptor antagonist) or finasteride (a 5 α -reductase inhibitor) resulted in significant improvements (reductions of 4 points) in American Urological Association Symptom Scores (AUASS) for LUTS associated with BPH, with a particularly pronounced effect with combination therapy (reductions of >7 points).^{10,11} Clinical progression of BPH (4 point increase in AUASS) was evident at 4 years in 4.6% (36 of 786) of men given combination therapy, 8.5% (65 of 768) of men given finasteride, 7.3% (55 of 756) of men given doxazosin, and 13.2% (97 of 737) of men given placebo,¹⁰ suggesting that, although generally effective, medications that target androgen receptor activity or smooth muscle contraction do not target all of the mechanisms that contribute towards LUTS. Although both surgical and medical approaches can improve urinary flow, such treatments are not effective for all men, can produce adverse effects that result in discontinuation of the therapeutic regimen, and do not abrogate the risk for disease progression.¹ Pathobiology other than androgen-mediated proliferation and smooth muscle dysfunction might, therefore, contribute to the development and progression of LUTD (Figure 1).

Inflammation and LUTD

Prostatic inflammatory infiltrate

Inflammatory infiltrates are very commonly observed in prostate tissue specimens from men with BPH and LUTS, and comprise about 70% T lymphocytes, 15% B cells, and 15% macrophages, as well as a smaller subpopulation of mast cells.^{10–12} Resident T-lymphocyte populations in prostate tissues actively secrete a diverse array of chemokines into the surrounding micro-environment. Immunohistochemical studies examining the histopathology of BPH have reported the presence of inflammatory infiltrate containing leucocytes associated with acute or chronic inflammation (or both).^{12–14} Neutrophilic or lymphocytic infiltrates were identified in 90% of transurethral resections of the prostate (TURP) specimens from 80 patients with BPH or LUTS but no history of prostatitis or prostatic infection.¹² Chronic inflammatory infiltrate was also detected in 30–60% of 1,197 randomly selected men with BPH or LUTS recruited to the MTOPS study. Patients with chronic inflammatory infiltrate had larger prostate volumes and were more likely to

experience clinical progression and acute urinary retention than those with no evidence of inflammation.¹³ A prospective study of 167 autopsied prostates identified 93 glands that harboured evidence of BPH; 75% of these glands contained inflammatory infiltrate (predominantly associated with chronic inflammation) compared with 50% of glands without signs of BPH and 55% of glands with evidence of cancer (Box 1).¹⁴

Prostatitis and UTI

Another source of inflammation and inflammatory damage to the lower urinary tract is prostatitis. Several epidemiological studies have demonstrated an association between prostatitis and subsequent development of LUTD. Data from the Health Professionals Follow-up Study showed a significant association between history of gonorrhoeal infection or young-onset (aged <30 years) prostatitis and later development of LUTS.¹⁵ The Olmsted County Men's Health Study showed that men with physician-diagnosed prostatitis were significantly more likely to develop prostatism, BPH, LUTS, or an enlarged prostate ($P < 0.0001$), receive treatment for BPH or LUTS ($P < 0.0001$), and develop acute urinary retention ($P = 0.01$) than those without a physician diagnosis of prostatitis. Moreover, even after adjusting for age and number of baseline physician visits, men with physician-diagnosed prostatitis were also more likely to receive subsequent treatment for BPH or LUTS.^{16,17} Combined data from five studies involving a total of 10,617 men suggest that men reporting a history of prostatitis have a substantially increased risk of developing BPH, LUTS, and prostate cancer.¹⁸ UTIs are also associated with male LUTD. In one study of 208 patients with bacteriuria, 54% were diagnosed with UTIs and these patients demonstrated voiding dysfunction manifested by higher rates of dysuria ($P = 0.0001$), urgency ($P = 0.0001$), and frequency ($P = 0.0001$; Box 1).¹⁹

Inflammation associated with ageing

Prostatic inflammation also results from the normal process of ageing. Significantly greater concentrations of interleukin-8 and the closely related C-X-C motif chemokine (CXCL) 5 are secreted by stromal fibroblasts cultured from the prostates of older men compared with younger men.^{20–22} Moreover, the secretion of interleukin-8, CXCL5, CXCL1, CXCL6, and CXCL12 by ageing prostate stroma induces proliferative responses from both epithelial and stromal prostate cells *in vitro*.^{21–23}

A likely source of CXCLs is senescent cells within the prostate tissue microenvironment. Many types of mammalian cells—with the exception of cells in continually renewing tissues originating from particular types of stem cells—become growth-arrested (senescent) over time. By definition, senescent cells are nonreplicative. Cells become senescent when their chromosomal telomeres become too short to permit further DNA synthesis and cell division. Such cells have effectively reached replicative exhaustion and entered replicative senescence. Cells might also become senescent under conditions of stress, which often results in DNA damage and growth arrest. Although these cells have not reached their Hayflick limit, they are nonreplicative and have entered cellular senescence. Many studies have shown that senescent cells accumulate with age *in vivo*.^{24–28} Studies have shown that senescing fibroblastic and epithelial cells secrete a medley of inflammation-associated proteins, including interleukins and chemokines (CC-type and C-X-C motif).^{29,30} The

Senescence Associated Secretory Profiles (SASPs) identified in these two studies were remarkably similar and corroborated with those previously identified for senescent prostate stromal fibroblasts and cells isolated from ageing and enlarged human prostates.^{20,21,31,32}

Other studies have shown that myofibroblast-rich reactive stroma characterizes hyperplastic, dysplastic, and neoplastic-associated prostatic stroma,^{33,34} BPH nodules exhibit elevated epithelial CXCL8 immunoreactivity (commonly associated with reactive stroma),³³ CXCL8 induces the differentiation of fibroblasts to myofibroblasts,³³ and overexpression of a keratinocyte-derived chemokine (the mouse homologue of CXCL8) in mouse prostatic epithelium can produce hyperplastic prostate epithelial acini (typically associated with a periacinar reactive stroma).³⁵ In addition, CXCL5, CXCL8, and CXCL12 promote the transition of normal prostate fibroblasts to myofibroblasts *in vitro*.³⁶ Taken together, these data suggest that an ageing inflammatory microenvironment might be conducive to myofibroblast accumulation and tissue fibrosis in the prostate. Thus, in the absence of comorbid disease processes, 'normal' ageing processes might suffice to promote fibrotic changes in lower urinary tract tissue architecture and consequent obstructive voiding symptoms (Box 1).

Inflammation associated with diabetes

A fourth source of inflammation that can potentially affect the lower urinary tract is type 2 diabetes mellitus (T2DM). Data from several recent epidemiological studies suggest that LUTD occurs more frequently among men with T2DM than in healthy controls.³⁷ Among 9,856 men with clinically diagnosed BPH, the presence of diabetes mellitus (13% prevalence) was associated with increased severity of LUTS, affecting voiding function more than storage function. Patients with BPH and T2DM had a significantly higher baseline International Prostate Symptoms Score (IPSS; 20.5 ± 0.2) and a significantly lower maximal urinary flow rate (Qmax; 10.4 ± 0.2) than those with BPH but without T2DM (18.6 ± 0.1 and 11.5 ± 0.1 , respectively; $P < 0.001$).³⁸ Indeed, it has been hypothesized that T2DM and LUTD share an underlying inflammatory pathogenesis as many important cytokines involved in inflammation are associated with both conditions.^{16,39}

An association between T2DM with LUTD initiation and progression has been biologically confirmed in animal models. Rabbits fed a high-fat diet (HFD) exhibited metabolic syndrome, as evidenced by hyperglycaemia and glucose intolerance, increased serum triglycerides and cholesterol levels, and increased mean arterial pressure (MAP) and visceral fat tissue (VAT).⁴⁰ These rabbits also developed bladder alterations (including fibrosis, hypoxia, and low-grade inflammation) in conjunction with reduced bladder compliance.^{40,41} Thus, a HFD was associated with metabolic syndrome, T2DM, inflammation, and urinary voiding dysfunction. Similar studies showed that HFD-fed SAMP6 and AKR/J mice developed diet-induced obesity and T2DM concurrently with increased VAT, prostatic inflammation, prostatic and urethral tissue fibrosis, and urinary voiding dysfunction.⁴² Taken together, these studies show that lower urinary tract inflammation is epidemiologically and biologically linked to tissue fibrosis and LUTD (Box 1).

Prostatic fibrosis

Tissue inflammation caused by ageing, infection, and other inflammatory disease processes is epidemiologically associated with the subsequent development of tissue fibrosis in multiple organ systems, leading to conditions such as pancreatic dysfunction,^{43,44} chronic obstructive pulmonary diseases,^{45,46} cirrhotic nonalcoholic fatty liver disease,^{47,48} and Crohn's disease.^{49–51} Mechanistically, fibrosis occurs downstream of inflammation (Figure 2), and can be considered as an inflammation-initiated, aberrant wound-healing process that is characterized by myofibroblast accumulation, collagen deposition, extracellular matrix (ECM) remodelling, and increased tissue stiffness.^{36,51–54} Tissue fibrosis impairs organ function by replacing normal tissue with highly collagenized scar tissue, increasing tissue stiffness (thereby reducing tissue elasticity and compliance), disrupting or ablating normal tissue innervation and vasculature.

Wound-activated ECM remodelling

Fibrosis can be regarded as an errant wound-healing process characterized by the activation and accumulation of myofibroblasts, which are transiently produced in many tissues as part of the normal wound response. Several cell types, including fibroblasts, pericytes, fibrocytes, and mesenchymal cells, might be capable of differentiating into myofibroblasts.⁵⁵ The common hallmarks of myofibroblast differentiation are expression of α -smooth muscle actin (α -SMA) and collagen type I, which is a large component of myofibroblast-secreted ECM. Myofibroblasts expressing α -SMA form focal adhesions to the surrounding collagen-augmented ECM, and contraction of these myofibroblasts provides the mechanical force needed for wound contracture and closure. Subsequent wound closure reduces the mechanical load on the myofibroblasts—potentially sensed by α -SMA, which is thought to be a mechanosensor protein—leading to dissolution of focal adhesions, the disassembly of α -SMA, and eventual myofibroblast apoptosis and cell death.^{53,54} If wound closure does not occur, myofibroblasts do not receive the mechanical signal to undergo apoptosis and continue to accumulate and deposit ECM, thereby replacing normal tissue with fibrotic tissue.

Prostate stromal fibroblasts can be induced to express fibrosis-associated collagen 1 and 3 and α -SMA, and to undergo complete functional myofibroblast phenoconversion in response to exposure to the canonical profibrotic protein TGF- β 1 or the CXCLs CXCL5, CXCL8, and CXCL12 (even in the absence of exogenous TGF- β 1).³⁶ Moreover, CXCL12-mediated myofibroblast phenoconversion can be completely abrogated by inhibition of the CXCL12 receptor CXCR4. These findings suggest that CXCLs, which comprise inflammatory proteins known to be highly expressed in the ageing prostate, can efficiently and completely mediate myofibroblast phenoconversion and might, therefore, promote the fibrotic changes in prostate tissue architecture that are associated with the development and progression of male LUTD.³⁶

Periurethral ECM deposition and fibrosis

A recent study of periurethral prostate tissues from 28 men used uniaxial load-unload mechanical testing to determine the mechanical stiffness of these tissues. Corresponding

tissue sections were digitally imaged and colour-segmented using a programme within MATLAB that separates and quantifies colour elements from images of tissues stained with Masson's trichrome, permitting quantitation of blue-stained areas corresponding to extracellular collagen. Periurethral prostate tissues from men with LUTS (>8 AUASI points) were significantly stiffer ($P = 0.0016$; pearson correlation $[r] = 0.82$) and demonstrated significantly greater collagen content ($P = 0.0038$; $r = 0.60$) and lower glandularity than tissues from men without LUTS (<7 AUASI points). In addition, histological inflammation was more pronounced in tissues with greater stiffness from patients reporting moderate or severe LUTS. When combined, these findings suggest that periurethral ECM deposition and fibrosis reduces urethral flexibility and compliance, thereby contributing to urinary obstructive symptoms and LUTS (Figure 3).⁵⁶

Therapeutic targeting of fibrosis

Standard of care

Several clinical trials have shown that patients who undergo radiation therapy to the prostate—a procedure that can induce tissue fibrosis or urethral strictures⁵⁷—demonstrate significant reductions in LUTS after treatment with α -adrenergic receptor antagonists.⁵⁸ Animal studies have shown that the ventral prostates of rats treated with the α -adrenergic receptor agonist phenylephrine are affected by interstitial fibrosis, inflammation, neoangiogenesis, and *de novo* synthesis of collagen (suggestive of a desmoplastic reaction).⁵⁹ Conversely, other studies have shown that the ventral prostates of adult Wistar rats treated with the α -adrenergic receptor antagonist doxazosin contain increased levels of collagen and collagen fibrils compared with untreated controls.⁶⁰ α -adrenergic receptor antagonists are known to target vascular and smooth muscle cells in the lower urinary tract. However, myofibroblasts, like smooth muscle cells, are contractile,⁵⁵ and further work is required to determine whether myofibroblasts respond to α -adrenergic receptor antagonists in a similar manner to smooth muscle cells in the lower urinary tract.

Several studies have documented histological changes in prostate tissue architecture—including increased levels of inflammatory infiltrate and fibrosis—after androgen deprivation therapy (ADT).^{61–63} Studies to examine prostate tissues from men treated with short-term or long-term 5 α -reductase inhibitor therapy for BPH or LUTS have not yet been conducted. However, given the association between tissue fibrosis and LUTD, such studies are warranted. Were ADT to be associated with myofibroblast phenocconversion and fibrosis in nonmalignant prostate tissues, such treatment might actually contribute to the progression of BPH and LUTS in some men.

Antifibrotic agents

If fibrosis is a pathobiology that contributes to LUTD, then antifibrotic therapeutic agents might be efficacious for treating men with LUTD, especially men who don't respond to 5 α -reductase inhibitors or α -adrenergic receptor antagonists. Surgical ablation of periurethral prostate tissues via conventional resection or MIST approaches is likely to ablate both proliferative and fibrotic tissues contributing to LUTD, thereby producing symptom relief. However, fibrosis is a recurrent condition and tissues from sequential resections should be

examined in order to determine whether resection provides durable symptom relief for men with periurethral fibrosis. Several humanized antibody or small molecule inhibitor antifibrotic therapeutic agents are currently in preclinical or clinical trials for conditions such as idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, renal fibrosis, hepatic fibrosis, cardiac fibrosis, dermal fibrosis, and other fibrotic diseases.⁶⁴ For example, pirfenidone, which targets TGF- β , is approved for the treatment of idiopathic pulmonary fibrosis in Japan and the European Union.⁶⁴ Therapeutics designed to inhibit the activities of particular inflammatory proteins, such as TNF- α (etanercept), interleukin-13 (QAX576), and CCL2 (CNTO-888), are in phase II clinical trials.⁶⁴ These novel agents are designed to interfere with the activities of particular proteins that promote myofibroblast phenoconversion or ECM production, including TGF- β 1, connective tissue growth factor, lysyl oxidase, interleukins, CC-type chemokines, integrins, and signalling proteins (for example, JNK and Jak2).⁶⁴ Some of these agents might prove useful for treating fibrosis-promoted LUTD in men who have failed current standard-of-care therapeutic or surgical ablation approaches. Treatment modalities do not need to be systemic as targeted modalities can be efficiently delivered to tissues of the lower urinary tract via instillation into the bladder or injection into the prostate ('reverse' biopsy).

In summary, tissue inflammation resulting from ageing, infection, or other inflammatory disease processes (for example, T2DM) is associated with the subsequent development of tissue fibrosis in the prostate. Periurethral prostate tissue fibrosis is, in turn, associated with LUTD, suggesting that fibrosis might be a previously unrecognized pathobiology that contributes to LUTD. Thus, antifibrotic therapeutic agents should be considered as a new approach to efficaciously treating men with LUTD, especially those who don't experience durable responses to 5 α -reductase inhibitors, α -adrenergic receptor antagonists, or surgical ablation.

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Sources of inflammation

- Inflammatory infiltrate
- UTI
- Prostatitis
- Ageing
- Type 2 diabetes mellitus

Figure 1.

Prostatic pathobiologies that contribute towards lower urinary tract dysfunction. The prostate consists of ductal glands surrounded by fibromuscular stroma, which, in turn, surrounds the prostatic urethra. **a** | The ductal glands and fibromuscular stroma can separately or concurrently hyperproliferate, producing prostatic enlargement and urethral obstruction. BPH can be medically managed by 5 α -reductase inhibitors, which prevent the conversion of testosterone to its active form, dihydrotestosterone, leading to reduced levels of available dihydrotestosterone and prostate tissue proliferation. **b** | Myofibroblast phenoconversion and accumulation—and consequent ECM deposition in periurethral prostatic tissue (and possibly also adjacent tissues)—causes tissue stiffness and reduced urethral compliance in men with lower urinary tract symptoms. **c** | Smooth muscle within the prostate can exhibit dysfunctional contractility with consequent urinary voiding dysfunction, which can be medically managed with α -adrenergic receptor antagonists (which relax smooth muscle). Abbreviation: ECM, extracellular matrix.

Figure 2.

Contribution of inflammation and fibrosis to lower urinary tract dysfunction (LUTD). UTI, prostatitis, ageing, and type 2 diabetes mellitus are all sources of tissue inflammation that promotes fibrosis in the lower urinary tract. Periurethral tissue fibrosis, stromal or epithelial prostatic proliferation, and smooth muscle dysfunction can, alone or in combination, promote male LUTD. These three pathobiologies can occur concurrently in the same prostate gland.

Figure 3.

Myofibroblast phenoconversion and the initiation of fibrosis in the prostate. **a** | Healthy prostate tissue is comprised of diverse cell types, including fibrocytes, fibroblasts, epithelial cells, and endothelial cells, as well as others not shown here (for example, neurons and leucocytes). **b** | Many of these cell types can act as precursor cells that undergo myofibroblast phenoconversion upon exposure to profibrotic stimuli. Myofibroblasts accumulate and deposit excessive ECM, which replaces normal tissue with stiff noncompliant fibrotic tissue. Abbreviation: ECM, extracellular matrix.