W8: Chronic Fibrosis in Lower Urinary Tract Dysfunctions—Mechanisms and Therapeutic Options

Workshop Chair: Anthony Kanai, United States

12 September 2017 09:00 - 10:30

Start	End	Topic	Speakers
09:00	09:20	Clinical Implications of Fibrosis in Bladder Pathophysiology	Marcus Drake
09:20	09:40	Collagen, the Extracellular Matrix and Bladder Fibrosis	Lori Birder
09:40	10:00	Therapeutic Benefits of Anti-Fibrotic and Anti-Inflammatory Agents	Anthony Kanai
10:00	10:20	Consequences of Fibrosis on Detrusor Contractile Function	Christopher Fry
10:20	10:30	Discussion	All

Speaker PowerPoint Slides

Please note that where authorised by the speaker all PowerPoint slides presented at the workshop will be made available after the meeting via the ICS website www.ics.org/2017/programme. Please do not film or photograph the slides during the workshop as this is distracting for the speakers.

Aims of Workshop

This workshop will provide the latest information on the pathophysiology and clinical implications of chronic fibrosis in lower urinary tract dysfunction (LUTD) including radiation and ketamine cystitis, underactive bladder, bladder obstruction and congenital anomalies. The workshop will consider how changes to the quantity and subtype profiles of collagen and its deposition in the extracellular matrix (ECM) of the bladder wall will impact on changes to compliance, passive tension and active and spontaneous force generation. The therapeutic benefits and mode of action of antifibrotic agents, including the hormone, relaxin, in rescuing these pathological conditions will be presented.

Learning Objectives

1) Provide up to date information on the clinical implications of chronic fibrosis in LUTD.
2) Discuss mechanisms that contribute to inflammation, collagen deposition and alterations in the ECM leading to chronic fibrosis.
3) Show findings of the therapeutic benefits of anti-fibrotic agents to increase wall compliance and enhance contractile function of bladders with increased ECM deposition.
4) Consider the cellular pathways that regulate ECM deposition.

Learning Outcomes

After the course, attendees will have the latest clinical and scientific information on LUTD related to chronic fibrosis and their therapeutic options. The information could be applied to attendees' research programs or patient management strategies.

Target Audience

Scientists, urologists and other healthcare workers interested in new mechanistic concepts and treatments for chronic fibrosis in LUTD.

Advanced/Basic

Advanced

Conditions for Learning

None.

Suggested Learning before Workshop Attendance

None.

Suggested Reading

The following reviews are recommended as preparation for the workshop.

1) The bladder extracellular matrix. Part I: architecture, development and disease. Aitken *et al.*, Nat Rev Urol., 6:596-611, 2009. PMID: 19890339.

2) Management of radiation cystitis. Smit et al., Nat Rev Urol., 7:206-214., 2010. PMID: 20212517.

3) Prostatic fibrosis, lower urinary tract symptoms, and BPH. Rodriguez-Nieves *et al.*, Nat Rev Urol., 10:546-50, 2013. PMID: 23857178.

4) Detrusor underactivity and the underactive bladder: a new clinical entity? A review of current terminology, definitions, epidemiology, aetiology, and diagnosis. Osman *et al.*, Eur Urol., 65:389-98, 2014. PMID: 24184024.

5) Functional properties and connective tissue content of pediatric human detrusor muscle. Johal *et al.*, Am J Physiol Renal Physiol., 307: F1072-9, 2014. PMID: 25209864.

6) Possible pathophysiology of ketamine-related cystitis and associated treatment strategies. Jhang *et al.*, Int J Urol., 22:816-25, 2015. PMID: 26087832.

7) Antifibrotic actions of serelaxin - new roles for an old player. Samuel *et al.*, Trends Pharmacol Sci., 37:485-97, 2016. PMID: 26996448.

8) Modelling and treatment of radiation cystitis. Zwaans *et al.*, Urology, 88:14-21, 2016. PMID: 26571081.

9) Detrusor underactivity: clinical features and pathogenesis of an underdiagnosed geriatric condition. Taylor *et al.*, J Am Geriatr Soc., 54:1920-32, 2016. PMID: 17198500.

Other Supporting Documents, Teaching Tools, Patient Education *etc.*

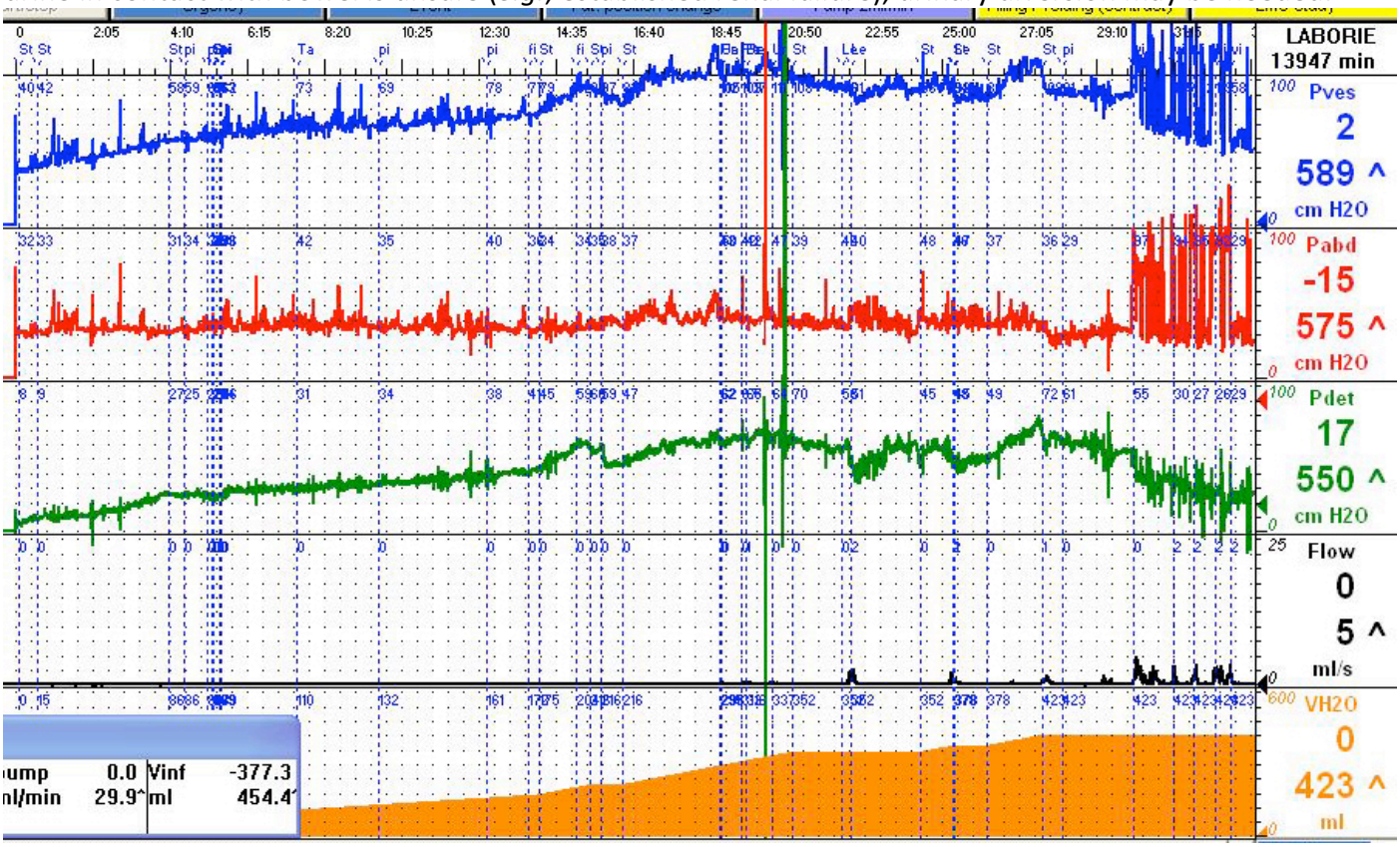
The following handout:

Clinical Implications of Fibrosis in Bladder Pathophysiology (M. Drake)

In urodynamic testing, the key feature of bladder filling is the low extent of pressure change across a wide volume range. This compliance property reflects the balance of active muscle relaxation and interspersed connective tissue (principally collagen and elastin) whose arrangements enable adaptive filling. In LUTD, compliance may be impaired in several situations. Sacral spinal cord dysfunction can show severe impairment of compliance which can be a risk for renal failure. Gross bladder wall thickening, notably in paediatric urological conditions, may also adversely affect compliance. A particular concern is chronic catheterisation, which can lead to severe loss of compliance and even absolute bladder capacity (measured under general anaesthetic). In the poorly compliant bladder, filling rate is extremely influential in the compliance assessment, such that conventional filling rate in neuro-urological cases is recommended to commence at only 10 ml/min. Compliance is typically measured and expressed as increase in bladder volume per centimetre of water increase in pressure (ml/cmH_2O), with as wide a volume as possible used to derive the parameter (typically start and end fill volumes). However, compliance is not necessarily even throughout filling; in some cases, there can be compliant filling up until a certain volume, above which the compliance can decline sharply; giving a single value for compliance may then not be an adequate description. The key implication of poor compliance is the potential for intravesical pressure to reach a value which could restrict emptying of the ureters. This will be determined by the resistance of the bladder outlet, with a weak outlet being safer, as the pressure is released (as a result of incontinence). Thus, the detrusor leak point pressure comes into substantial clinical significance in identifying long-term risk of renal dysfunction where it is 40 cmH_2O, or perhaps even lower.

In some cases, antimuscarinic medication (and perhaps beta-3 agonists) may partly counteract the compliance impairment, while onabotulinum-A toxin has proved helpful in many cases, and this presumably indicates (partial) recovery of the muscle property of adaptive relaxation. However, the environment of chronic infection, foreign body reaction, inflammation and loss of cycling appears to predispose to a worsening of connective tissue infiltration. There is no current approach in clinical use for restoring the connective tissue to a subordinate influence. Thus, the only approach to protect safe urine storage, where the reversible muscular contribution to impaired compliance is small, is reconstructive

surgery. This is achieved by cystoplasty, importing a bowel segment into the storage compartment to lessen the proportion of the bladder storing under adverse conditions. In severe cases or situations where urine in contact with bowel is unsafe (*e.g.*, established renal failure), urinary diversion may be needed.



FIGURE; Filling cystometry and pressure flow study of a man with spina bifida, showing bladder pressure (top), abdominal pressure, detrusor pressure, flow and filling volume (bottom). The bladder and detrusor pressure climb steadily in the first half of the trace, indicating poor compliance. Leakage occurs at a relatively high pressure; the detrusor leak point is at a pressure of about 60 cmH_2O, suggesting a high risk of renal problems.

Collagen, the Extracellular Matrix and Bladder Fibrosis (L. Birder)

The objectives of this presentation are to: 1) Describe specific orientations of collagen fibers in different layers of the bladder wall; 2) discuss collagen fiber and wall architecture during bladder loading; and 3) discuss how aging alters wall extensibility by premature recruitment.

Lower urinary tract symptoms (LUTS), in particular storage symptoms are a major health related problem in the elderly. There is little information to explain how aging alters normal bladder physiology and how these changes contribute to the aetiology of LUT disorders in the elderly. During aging, external and internal stressors perturb normal cellular homeostasis, causing progressive cellular and tissue decline. Our research has shown that aging correlates with altered urothelial expression of various mediators as well as changes within the ECM. Collagen and elastin fibers provide structural support as bladder smooth muscle stretches during bladder filling. Not only is the amount of these fibers important for proper bladder function, but also their orientation, conformation and recruitment during bladder filling. Collagen type III fibers (found in flexible and distensible tissues) display specific orientations with different bladder volume, which also differ according to location in the bladder. For example, when the bladder is relaxed, fibers appear as loose (wavy) networks with random orientation. During bladder expansion, fibers appear long and thin and lie parallel to urothelium and smooth muscle. This arrangement likely allows maximal bladder storage without imposing strain on the wall. In aging bladders, changes in the smooth muscle/collagen ratio and possibly ECM composition likely impair the orientation, conformation and recruitment of collagen fibers. New studies by our group using a combination of biaxial stretch and multiphoton imaging, have

shown that a coordinated recruitment of collagen across the lamina propria and detrusor layers is essential for the large elasticity of the bladder wall. Furthermore, wall extensibility can be lost (in the aged bladder) by premature recruitment of collagen fibers. This suggests that additional tension/stretch may be imposed on the urothelial cells and/or smooth muscle as the bladder fills. This can impair the communication between the urothelium and other cells in the bladder wall and account for symptoms of the aging bladder. Further studies are necessary to understand the biomechanical environment of the intramural cells that drive changes in the bladder wall in health and disease.

Therapeutic Benefits of Anti-Fibrotic and Anti-Inflammatory Agents (A. Kanai)

The objectives of this presentation are to: 1) Show findings on the therapeutic benefits of the hormone, relaxin, in preventing inflammation, reversing fibrosis and enhancing contractile functions to rescue bladders with chronic radiation cystitis and underactive bladders due to aging; 2) describe the mechanisms involved in relaxin therapy; and 3) discuss the therapeutic benefits of other agents, including the immunosuppressant tacrolimus, in treating fibrosis.

Relaxin is a 6kDa hormone, first described in 1926 (Hisaw, F.L., Exp. Biol. Med. 23:661, 1926), that is mainly produced by the corpus luteum in the ovaries to relax the uterus and soften the pubic symphysis during pregnancy, but also in the prostate and testes to enhance sperm mobility. It belongs to the insulin superfamily with seven members; relaxin-1 to -3 and insulin-like peptide-3 to -6. Relaxin is formed as a three chain pro-hormone, and when one chain is cleaved, it forms an active heterodimer with 24 and 29 amino acids linked by disulfide bridges. There are four G-protein coupled receptors (RXFP1-4), with RXFP1 being the most studied in humans and rodents and for which relaxin-2 (RLX2) has the highest affinity. These receptors have broad distribution in the CNS and periphery and they are therapeutic targets in heart, kidney, liver, lung and the portal vein. The data to be shown in this workshop are the first to describe that RXFP-1 and -2 are expressed in the urinary bladder and that treatment with recombinant human RLX2 (hRLX2) reverses fibrosis in mouse bladders with chronic radiation cystitis and in underactive bladders of aged rats.

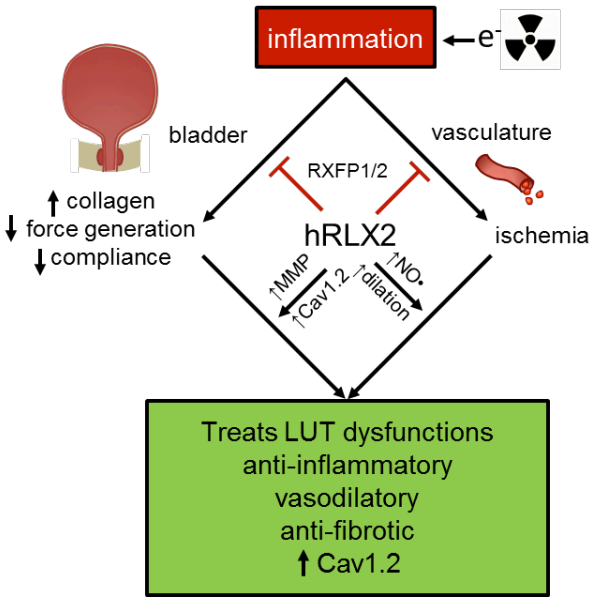


Figure. Consequences of radiation cystitis and the benefits of hRLX2 therapy. *One of the initial responses following radiation exposure is inflammation due to urothelial apoptosis and urine infiltration. Concurrently, there is damage to the vascular endothelium leading to ischemia. These processes cause increased collagen deposition, and decreased bladder compliance and force generation. Treatment with hRLX2 reverses fibrosis through inhibition of collagen synthesis and enhancement of its degradation by matrix metalloproteinases (MMP). It also enhances contractile function through increased Cav1.2 (i.e., L-*

type Ca^{2+} channel) expression and improved tissue perfusion via nitric oxide (NO·) induced vasodilation. hRLX2 is also anti-inflammatory, inhibiting recurrent damage to the bladder wall.

There are currently no pharmacological agents approved for treatment of fibrosis-induced lower urinary tract dysfunction. There are preventative treatments such as intravesical tacrolimus, a calcineurin inhibitor which has very potent anti-inflammatory actions. Hyperbaric oxygen therapy is utilized to treat acute radiation cystitis symptoms and may potentially prevent the development of ischemia-induced fibrosis by stimulating NO· synthase expression and angiogenesis.

Consequences of Fibrosis on Detrusor Contractile Function (C. Fry)

The objectives of this presentation are to: 1) Describe how the deposition of ECM changes in clinical conditions affecting the LUT; 2) discuss how fibrosis affects the contractile properties of muscular tissues of the LUT; 3) describe how extracellular chemical and physical factors change the function of fibroblasts; and 4) demonstrate novel advances in the regulation of ECM deposition.

The detrusor smooth muscle layer of the bladder wall is the principal tissue responsible for generating an increase of wall tension during voiding, and when relaxed contributes to the high compliance of the bladder during filling. However, this tissue contains a number of components in addition to smooth muscle, an important component of which is an ECM of collagen and elastin. The biomechanical properties and the relative quantity of the ECM will have profound effects on the contractile properties of the bladder wall. During detrusor contraction, force generated by the muscle cells will be transmitted through this ECM, which will impart its own influence on the magnitude and temporal profile of tissue contraction. When the detrusor is relaxed, changes to passive wall tension during filling will be importantly affected by the biomechanical properties of the ECM itself and contribute to bladder compliance.

Many LUT pathologies are characterised by an increased deposition of ECM – fibrosis. This results in thickening of the affected tissue and such scarring may be regarded as an exaggerated wound healing response. In the LUT, clinical conditions producing fibrosis include: bladder outflow obstruction, detrusor overactivity, congenital anomalies and chronic inflammation; as well as imposition from external agents such radiation, raised intravesical pressure and certain drugs.

A principal source of ECM is the fibroblast and transformed phenotypes including myofibroblasts. A key consideration is to understand the external agents that influence these cells to generate ECM and also to consider how fibroblasts themselves acting in an autocrine or paracrine fashion through their secretion of profibrotic factors.