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Collaborative Review – Voiding Dysfunction

A Refocus on the Bladder as the Originator of Storage Lower Urinary Tract Symptoms: A Systematic Review of the Latest Literature

Alexander Roosen[a,*], *Christopher R. Chapple*[b], *Roger R. Dmochowski*[c], *Clare J. Fowler*[d], *Christian Gratzke*[a], *Claus G. Roehrborn*[e], *Christian G. Stief*[a], *Karl-Erik Andersson*[f]

[a] *Department of Urology, Ludwig Maximilians University, Munich, Germany*
[b] *The Royal Hallamshire Hospital, Sheffield, UK*
[c] *Vanderbilt University Medical Centre, Nashville, TN, USA*
[d] *The National Hospital for Neurology and Neurosurgery, London, UK*
[e] *The University of Texas Southwestern Medical Centre, Dallas, TX, USA*
[f] *Wake Forest Institute for Regenerative Medicine, Winston Salem, NC, USA*

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Abstract

Context: The focus of clinical understanding and management of male storage lower urinary tract symptoms (LUTS) has shifted from the prostate to the bladder. This is mirrored by an increasing body of experimental evidence suggesting that the bladder is *the* central organ in the pathogenesis of LUTS.
Objective: A systematic review of the literature available on pathophysiologic aspects of storage LUTS.
Evidence acquisition: Medline was searched for the period ending December 2008 for studies on human and animal tissue exploring possible functional and structural alterations underlying bladder dysfunction. Further studies were chosen on the basis of manual searches of reference lists and review papers.
Evidence synthesis: Numerous recent publications on LUTS pathophysiology were identified. They were grouped into studies exploring abnormalities on urothelial/suburothelial, muscular, or central levels.
Conclusions: Studies revealed both structural and functional alterations in bladders from patients with LUTS symptoms or animals with experimentally induced bladder dysfunction. In particular, the urothelium and the suburothelial space, containing afferent nerve fibres and interstitial cells, have been found to form a functional unit that is essential in the process of bladder function. Various imbalances within this suburothelial complex have been identified as significant contributors to the generation of storage LUTS, along with potential abnormalities of central function.

* Corresponding author. Department of Urology, Ludwig Maximilians University, Marchioninistrasse 15, 81377 Munich, Germany.
E-mail address: a_roosen@hotmail.com (A. Roosen).

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1. Introduction

In 2009, we now recognise that lower urinary tract symptoms (LUTS) do not reliably reflect the underlying vesicourethral pathology; hence, the bladder is sometimes referred to as an "unreliable witness." The term *LUTS* encompasses three groups of symptoms: voiding (slow stream, splitting or spraying, intermittency, hesitancy, straining, terminal dribble), postmicturition (sensation of incomplete emptying, postmicturition dribble), and storage. These symptoms are often described by the term *overactive bladder* (OAB): urinary frequency, nocturia, urgency, and urgency urinary incontinence [1].

Voiding symptoms have been reported to be the most common LUTS in men. However, women also commonly present with voiding symptoms [2,3].

Likewise, storage symptoms are not sex specific but increase in an age-related fashion and are prevalent in both male and female patients. Indeed, there is a similar distribution of both storage and voiding symptoms [4]. This paradigm shift in our clinical understanding and evaluation of LUTS [5–7] is mirrored by an increasing body of experimental evidence suggesting that the bladder has to be considered *the* central organ in the pathogenesis of LUTS.

2. Evidence acquisition

Medline was searched using the terms *overactive bladder, detrusor overactivity, lower urinary tract symptoms, pathophysiology,* and *ageing bladder* for dates up to December 2008. Further studies were chosen on the basis of manual searches of reference lists and review papers and from meetings of the International Continence Society, the European Association of Urology, and the American Urological Association. This approach was chosen because previous work has shown that manual search improves the database search.

3. Evidence synthesis

Whereas voiding symptoms are only poorly correlated with bladder outlet obstruction (BOO), storage symptoms have a closer association with underlying detrusor overactivity (DO) [5]. To date, three theories, each of which probably contributes in varying proportion to the complex mechanisms underlying the genesis of DO and the associated storage symptoms composing OAB, have been put forward:

- The *urothelium-based* hypothesis: Changes in urothelial receptor function and neurotransmitter release as well as in the sensitivity and coupling of the suburothelial interstitial cell network lead to enhancement of involuntary contractions [8].
- The *myogenic* hypothesis: Changes to the excitability and coupling of smooth muscle cells with other myocytes or interstitial cells lead to the generation of uninhibited contractions [9,10].
- The *neurogenic* hypothesis: Reduced peripheral or central inhibition increases activation of the micturition reflex and involuntary bladder contractions [11]. Peripherally, neurologic diseases might cause a sensitisation of C fibres that are silent under normal circumstances, thereby leading to the emergence of a C-fibre-mediated reflex.

This paper provides an overview of the contemporary evidence base on the structural and functional changes in the bladder of patients suffering from storage LUTS.

3.1. Changes on the urothelial and suburothelial level

In contrast to the classical view of the urothelium as merely a passive barrier to ions and solutes, the urothelium has increasingly been recognised to have an important secretory function that allows it to undertake a neuromodulatory role. In support of this, both the urothelial metabolic rate and receptor density are higher than that of the detrusor [12]. The urothelium interacts closely with the underlying suburothelial layer, in particular the interstitial cell network contained within it, so that the whole structure can be regarded as a functional unit [8]. The urothelium is composed of three sublayers: a basal layer attached to the basement membrane, an intermediate layer, and an apical layer of large hexagonal cells referred to as umbrella cells. The suburothelium is an area composed of nerves, blood vessels, and connective tissue in intimate contact with the urothelium.

3.1.1. Urothelial sensory functions and changes in disease

Histologic studies have shown that urothelial cells themselves express sensory receptors typically found on primary afferent nerves. One example is the transient receptor potential cation channel subfamily vanilloid member 1 (TRPV1) [13,14]. TRPV1, a sensory receptor widely distributed throughout the body, is activated by heat and protons. Liu et al reported that urgency is associated with increased TRPV1 expression in the human bladder trigonal mucosa [15]. Several studies on TRPV1-null mice suggest a role for TRPV1 receptors both in inflammatory conditions [16] and during normal voiding function [17,18]. Bladder biopsies from patients with both idiopathic detrusor overactivity (IDO) [19] and neurogenic detrusor overactivity (NDO) [20] showed increased urothelial TRPV1 expression. The agents capsaicin and resiniferatoxin act on vanilloid receptors, thereby producing epithelial desensitisation by turning them less reactive to natural stimuli as well as neural degranulation and damage [21,22]. They have been shown to reduce urgency and bladder pain [23] along with urothelial TRPV1 immunoreactivity. Whether or not TRPV4, another member of the TRP receptor family that is expressed by the urothelium and has been shown to be involved in normal voiding behaviour, has a role in bladder dysfunction remains to be elucidated [24,25].

Both P2X and P2Y purinergic receptor subtypes have been identified in the bladder urothelium. It is now thought that these may respond to urothelial-derived adenosine triphosphate (ATP) release in autocrine and paracrine