Perspective

Coining a new term-Urovesicology: advancing towards a mechanistic understanding of bladder symptoms

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Introduction

When patients present with lower urinary tract symptoms (urgency, frequency, nocturia, slow stream, hesitancy, sense of incomplete emptying, post-void dribbling), urinary incontinence (stress and urge), urinary retention, dysuria, and/or bladder pain, the urologist would be the most appropriate specialist to evaluate and treat these patients. These symptoms will be collectively labeled as "urovesicologic" symptoms, the reason which will become apparent. Because these symptoms usually have no known cause, empiric (trial-and-error) treatments directed at ameliorating symptoms, but not at the underlying pathophysiology, are the usual recourse.

Within the field of urology, there are numerous appellations given to those who treat urovesicologic symptoms. These appellations, to date, include female urologist, female pelvic medicine and reconstructive surgeon, urogynecologist, neurourologist, urodynamicist, and probably a few more. Why so many? Of course, there are specific reasons. Labels with the words "female" or "gyn" imply that these subspecialists focus only on female patients. The use of the words "medicine" and "surgeon" imply that the physician has both intellectual and technical skills. The label "neuro" implies expertise in treating urologic issues in patients with concomitant neurologic diagnoses such as spinal cord injury, multiple sclerosis, post-cerebrovascular accident (stroke), Parkinsons, and Alzheimers, which can adversely affect bladder function. The term "urodynamicist" implies an expert in urodynamics with the further implication that urodynamics can objectively determine the etiology of the urovesicologic symptoms and/or prognosticate treatment outcomes.

Ultimately, how do these numerous labels help patients with these urovesicologic symptoms? Do we even need these many labels? The critical issue is the lack of understanding of how physiologic function/dysfunction translates into symptoms. We should not be so focused on a specific gender, treatment modalities (medicine versus surgery), distinct concomitant disease (neurogenic versus non-neurogenic) or ability to do specialized testing (urodynamics). The urologists should be the specialty that seeks knowledge about the pathophysiologic mechanisms underlying urovesiciologic symptoms.

Therefore, I propose a new term, "urovesicology" (uro=urine + vesic=bladder + ology=study of) which would be a discipline that studies basic pathophysiologic mechanisms that lead to bladder symptoms. Urovesicology will not be limited to mechanisms based on a gender (male or female), a specific treatment method (medical or surgical), a specific cause (neurologic injury or degeneration) nor a specific testing modality (urodynamics), but rather, urovesicology would be defined by development and implementation of new treatments and/or diagnostic tests for urovesicologic symptoms based on ability to measure, detect, and/or quantify specific pathophysiologic mechanisms. Future treatments will therefore be driven by mechanistic principles rather than the current paradigm of empirical symptoms-based treatment. This editorial will present what the future in urovesicology might hold.

Future of urovesicology research from the neurophysiologic level

Current treatments for urovesicologic symptoms that target the nervous system include: (I) Implantable sacral neuromodulation (1,2) (II) Posterior tibial nerve stimulation

(3,4) (III) Onabotulinumtoxin A detrusor injection (5,6). These therapies impact the neurophysiologic control of bladder function. Electrostimulation of the sacral 3rd nerve root and posterior tibial nerve may work through modulation of central organization of afferent signals to impart symptomatic relief. Functional positron emission tomography (PET) data show that the blood flow patterns (surrogate marker for neural activity) to certain areas in the brain are altered in the patients with idiopathic urge incontinence and furthermore are altered during InterStim treatment (7). Other studies using functional MRI (fMRI) in normal and urge incontinent subjects suggest that urge incontinence is associated with measureable changes in brain activities (8,9). fMRI might be useful as a diagnostic test in order to stratify patients to treatment options. By understanding brain function and its relationship to urovesicologic symptoms, future treatments might be able to target these central neural projections, although treatments targeting the central nervous system (CNS) would likely have to clear a high bar in terms of safety.

Intradetrusor injections of onabotulinum toxin A prevent the release of acetylcholine by the pre-junctional motor nerve terminals thereby preventing contraction of detrusor muscle. The USA Food and Drug Administration (FDA) just recently approved the use of intradetrusor injections of onabotulinum toxin A (BoTox™) for neurogenic detrusor overactivity incontinence secondary to multiple sclerosis and spinal cord injury (5). Therefore, this is the first approved use of pharmacologic neuromodulation (as opposed to electrical neuromodulation) for treatment of a urovesicologic symptom related to neurologic diagnoses. Additionally, there is evidence that this toxin is efficacious for non-neurogenic (i.e. idiopathic) urgency urinary incontinence and urinary frequency (6).

A better understanding of bladder afferent signaling mechanisms may also bear fruit. Understanding chronic bladder pain (aka interstitial cystitis/painful bladder syndrome) as form of central nervous system sensitization (10) may unlock mechanistic processes that can be therapeutically targeted. Another related issue is how pelvic organ cross-innervation can modulate afferent signals from different pelvic organs (11,12) leading to various pelvic symptoms. Urinary urgency, frequency and bladder pain are sensory problems and therefore, a better understanding of the afferent mechanisms will lead to more efficacious treatments. Measurement of bladder afferent function using current perception thresholds (CPT) in asymptomatic women have been published (13). Interestingly, bladder CPT testing showed that a change in bladder sensation was not correlated with occurrence of detrusor overactivity detected on urodynamics (14) suggesting that detrusor overactivity may not necessarily be related to the sensation of urgency.

Non-obstructive urnary retention is a poorly understood clinical problem. Whether this is from neurogenic and/or myogenic failure is unknown. For patients with urinary retention secondary to neural compromise from spinal dysraphism, nerve re-routing (somatic-to-autonomic motor connection) has been described to normalize bladder motor function although this therapy has engendered controversies (15,16). Whether or not nerve re-routing can be applied to patients without neurologic defects (idiopathic non-obstructive urinary retention) would depend on whether the cause of the retention is primarily neurogenic or myogenic failure.

Urovesicologic symptoms secondary to spinal cord injury (SCI) is a major issue in long-term care. Philosophically, it can be argued that the best approach to addressing all of SCI-related problems is to discover how to regenerate spinal cord neurons so that SCI-patients can be cured of their injury. The use of embryonic stem cells injected intrathecally to regenerate neurons has been studied in animal models of SCI (17). The first clinical trial for use of human embryonic stem cells in treating acute spinal cord injury was recently stopped after 4 SCI patients were enrolled due to entrepreneurial economic reasons (18). Whether stem cell therapy in SCI would also normalize bladder function remains unknown.

Socially acceptable bladder control is a behavioral and cognitive event that occurs during toilet training age. The strong connections between the brain and bladder have led some to equate bladder behavior with emotions and the soul (19). Along this paradigm, it has been suggested that corticotropin releasing factor (CRF) has a role as a mediator of emotional influences on bladder function (20). This association has been born out in animal studies of voiding behavior in social stress situations. There were changes in electrical activity of neurons in the locus coeruleus in the brain (21) and bladder wall remodeling (22) which are under the control of CRF (23). Whether CRF can be used for urovesicologic symptoms remains to be seen.

In the future, will we ultimately be able to detect an abnormal neurophysiologic signal in patients with urovesicologic symptoms who currently have no measureable neurologic deficits? How will this signal be measured? Will we have a treatment that normalizes this signal? Where in the CNS will this signal be – the peripheral or central nervous system? The answers will come with continued research.

Future of urovesicology research at the bladder level

The main method to study bladder physiology for many years has been to focus on bladder (detrusor) smooth muscle. Much of the work has been to explore mechanisms to block unwanted detrusor contractions that presumably underlie the pathophysiology of urgency urinary incontinence. Fewer studies have addressed molecular causes of smooth muscle contractile failure and whether idiopathic non-obstructive urinary retention could be related to these mechanisms. This traditional research paradigm on blocking contractility led to oral antimuscarinics in treating urinary frequency, urgency, nocturia and urge incontinence. So while antimuscarinics represent a viable treatment option, they are not uniformly effective and have bothersome side effects. Patients do not stay on these medications long term. As in almost all treatments for urovesicologic symptoms, use of antimuscarinics requires no detailed understanding of pathophysiology underlying symptoms in an individual patient.

A new paradigm for the function of the bladder urothelium is its role in regulation of bladder function (24). Investigators have suggested that the bladder urothelium may be a key regulator of bladder afferent signaling through crosstalk with suburothelial and intra-urethral sensory nerve fibers. This is opposed to the notion that bladder afferent signaling arise only from the afferent nerves. Bladder urothelial cells are known to release neurotransmitters in response to stretch and also express receptors that are typically found on neurons. Some have proposed that the site of action of antimuscarinics may not only be on detrusor smooth muscle, but also on the urothelium. Suburothelial myofibroblasts, which are located just underneath the urothelium, are specialized cells which are thought to regulate spontaneous detrusor contractions (25,26). Can future therapies target the bladder urothelium to specifically reverse a urothelial physiologic abnormality? Can cystoscopy in the future incorporate new imaging techniques to be able to visualize urothelial abnormalities to help in diagnosis in patients with urovesiologic symptoms? The answers will depend on whether the new paradigm of urothelial function is true or not.

The urothelium also plays a key role in preventing bacterial invasion of the underlying stroma. While many researchers are interested in bacterial virulence factors, fewer are interested in host defense factors which the bladder urothelial cells play a central role. For example, the host response to bacterial pathogens is initiated by bacterial lipopolysaccharide (LPS) interaction with the Toll-like receptor 4 (TLR4) on the bladder urothelial cell. Activation of TLR4 stimulates cytokine release from bladder urothelial cells which can lead to activation of the immune system resulting in a robust host defense against the offending bacteria (27). Understanding host urothelial responses would be critical in being able to leverage this understanding in reducing urinary tract infection (UTI) perhaps without antibiotics.

The future of bladder specific therapies depends on whether urovesicologic symptoms arise directly from the bladder compartments (urothelium, suburothelium, nerves, smooth muscle) or whether symptoms arise secondarily from other conditions and diseases such as neurologic diseases (e.g., SCI, multiple sclerosis, stroke, etc.), metabolic syndrome (see later section), bladder outlet obstruction, and/or urethral/pelvic floor (bladder outlet) pathology (see later section).

Future of urovesicology from the urethra/pelvic floor level

The urethra, urethral sphincteric complex and pelvic floor muscles comprise the bladder outlet. The motor function of the bladder and the urethra/pelvic floor must act in opposite fashions. During storage, bladder is relaxed whereas the urethra/pelvic floor is contracted, during emptying, bladder is contracted whereas the urethra/pelvic floor is relaxed. The knowledge of urethral and pelvic floor function is even less than the knowledge of bladder function. Perhaps the urovesicologic condition that best exemplifies our lack of understanding of basic urethral function is female stress urinary incontinence (fSUI). We have been treating fSUI for many years and yet our treatment is still not directed at reversing urethral sphincter pathophysiology. Furthermore, we have no tools to identify specific mechanisms that underlie urethral pathology leading to fSUI. Whether fSUI is caused by an anatomic lack of support of the urethra (i.e. urethral hypermobility) versus lack of intrinsic urethral function (i.e. lack of neuromuscular function, lack of vascularity, lack of urethral coaptation) has been argued for decades. It is argued that intrinsic urethral function, not loss of anatomic support, is the primary basis of fSUI (28). A recent study suggests that fSUI is due to a neuromuscular defect, as measured by EMG, of the female urethral sphincter (29). Furthermore, duloxetine, an agent that can increase urethral sphincteric tone via increased efferent activity from Onuf's nucleus, was found to be efficacious in fSUI (30). Despite these and other findings, our current treatment is still based on an anatomic-based treatment

(midurethral sling) which partially obstructs the bladder outlet. It is conceivable that the sling could correct the neuromuscular function of the urethra, but the mechanical advantage (e.g., backboard or hammock effect) of the sling is likely the primary reason for its beneficial effect.

While detrusor overactivity has been traditionally described as the pathophysiology of overactive bladder (OAB), investigators have wondered whether urethral sensory dysfunction plays a role in OAB. What is interesting is that urethral sensation appears to be decreased in OAB and furthermore, the sensation in the urethra increased after treatment with tolterodine (31). The concept that the female urethral physiologic disturbances may play a role in urovesicologic symptoms is not new, especially with the previous nomenclature of "female urethral syndrome" (32). We will also require a better understanding of the role of the pelvic floor musculature in bladder function. Studies have framed urovesicologic symptoms in the context of pelvic floor myofascial disorders, both in males and females (33-35). Treatments to relax pelvic muscles have resulted in reduction of urovesicologic symptoms.

The interesting, yet potentially difficult, aspect of treating urovesicologic symptoms is the ying-yang relationship between the bladder and its outlet (urethra/pelvic floor) from the motor (efferent) perspective. Normal functioning of the lower urinary tract requires complementary yet opposite functions of the muscles comprising the bladder and urethra/pelvic floor. During urinary storage, there should be no urinary incontinence with the bladder relaxed, and the urethra contracted. During micturition, the bladder contracts while the urethra relaxes resulting in maximum emptying efficiency. Therefore treatments directed at the motor function of the urethra and pelvic floor have to take into account this inverse relationship with the bladder. However, while motor functions of the bladder and urethra are necessarily contradictory, the sensory (afferent) functions of the bladder and urethra/pelvic floor are not, with constant sensory signals from the lower urinary tract flowing into to the central nervous system. Leveraging our understanding of the mechanisms underlying urethral/pelvic floor sensation into viable treatment options for urovesicologic symptoms will be important in the future.

Future of urovesicology from genomics/proteomics and biomarkers level

For diseases in which the pathophysiologic mechanisms are poorly understood, genomics and proteomics technologies allow researchers to probe for possible etiologies. Genetic investigational tools such as genome-wide association study (GWAS) can localize potential gene loci related to cause of urovesicologic symptoms by comparing symptomatic versus non-symptomatic (control) patients. However, several difficulties lie with this type of approach. First, accuracy of GWAS requires a homogenous afflicted population (phenotype). Phenotyping patients who have urovesicologic symptoms are neither uniform nor completely objective. Patients often have more than one type of lower urinary tract symptoms and there is high degree of overlap of symptoms making a "pure" phenotype difficult. Second, the interaction of many genes complicates the ability to detect a clean signal; none of the urovesicologic symptoms is thought to be due to a single-gene defect. Third, finding a significant association between a disease and loci within the genome does not mean that the gene products and/or function of the gene products within these loci will be known. Another approach would be to compare the genome of responders versus non-responders (or poor-responders) to a particular therapy in hopes of finding a genetic signal that underlies response to treatment. This approach would not require a specific phenotype for the cases and may still shed light on the pathophysiologic mechanisms underlying the cases.

As genetic tools advance and statistical abilities to analyze large datasets improve, genetics-based research may pay off. It is hoped that the end result of these approaches is a mechanistic based treatment for urovesicologic symptoms. While peer-reviewed original research in this area is sparse, a recent review of what the future holds for genetic studies for urovesicology has been published (36).

Proteomics examines the entire protein expression profile using high throughput technologies such as mass spectroscopy. A pilot study of urinary proteomics in interstitial cystitis/painful bladder syndrome (IC/PBS) has been published; this study showed differences in urinary protein expression profiles between cases (IC/PBS) and controls (37). Taking a different approach, another investigative group has examined proteomics at a cellular level by examining the effects of the putative causal factor for IC/PBS, antiproliferative factor (APF) (38). These investigators mapped out protein increases/decreases that APF induced within a cell. Based on bioinformatic network analyses of APF-induced protein changes, the authors identified the β-catenin network as a central pathway regulated by APF (39) suggesting a mechanism of action for APF. How will urinary proteomics change urovesicology in the future? It is uncertain, but a PubMed review of the terms "urinary proteomics and bladder cancer" revealed

95 publications suggesting that urinary proteomics is on its way to becoming an integral part in bladder cancer management. Given the rapid advances in technology, both in terms of throughput analysis (e.g., mass spectroscopy) and data analyses algorithms (e.g., statistical methodologies coupled with computing speed), urinary proteomics could be easily applied to urovesicology to elucidate pathophysiologic mechanisms underlying urovesicologic symptoms which would lead to novel treatments.

Proteomics should eventually identify candidate proteins of interest. However, one urinary protein, nerve growth factor (NGF), which was not identified with proteomics, has been studied by extensively by one research group as a possible biomarker for OAB (40). The origin of the increased NGF in the urine from OAB patients is not known; it can be from the urothelium, nerves or even perhaps the upper urinary tract. It was shown that bladder urothelial tissue levels of NGF was similar between subjects with detrusor overactivity versus those without detrusor overactivity (although all subjects had OAB symptoms) (41) suggesting that the source of urinary NGF might not be the bladder urothelium. On the other hand, there is a transgenic mouse model of conditional NGF knock-in where NGF overexpression is restricted to bladder urothelium. These transgenic animals had significantly increased voiding frequency, increased mast cells in bladder wall, and increased pelvic hypersensitivity (42). A monoclonal antibody to NGF (tanezumab) has been tested for IC/PBS (ClinicalTrials.gov identifier NCT00999518), but the results have not been published. Urinary NGF changes has also been correlated with treatment outcomes (43) suggesting decreased urinary NGF with successful treatment of urinary symptoms with antimuscarinic therapy. Similarly, urinary NGF was decreased after successful treatment of IC/PBS (44).

Another set of urinary biomarkers under investigation is that of epidermal growth factor (EGF), heparin-binding epidermal growth factor-like growth factor (HB-EGF) and APF in IC/PBS. These 3 markers have been found to be the most useful in delineating the phenotype of IC/PBS (45). However, these urinary markers have not been associated with other pathologic findings from bladder biopsies, presence of ulcers on cystoscopy (46) or response to treatment (albeit it a negative treatment trial) (47).

The future of urovesicology will parallel other clinical disciplines if urologic investigators apply the rapidly advancing technologic tools of genetics, proteomics and biomarkers. Personalized medicine, based on each individual's genomic sequence, may one day help predict biologic responses to treatment, and/or identify risk factors associated with treatment failure. Discovery of biomarkers that help diagnose, prognosticate response to treatments, and/or help with treatment selection will brighten the future of uroveiscology.

Future of urovesicology from tissue engineering/ stem cell level

The promise of stem cells in urovesicology is exemplified by the use of striated-muscle derived stem cell injections into urethral sphincter for treatment of fSUI (48,49). However, no FDA-approved stem cell therapy for fSUI exists today. A recent review of this topic suggests that there are roadblocks to overcome including validity of animal models and multilineage differentiation of the injected stem cells (50).

Tissue engineering, where a biological neobladder was grown in laboratory and successfully augmented into neurogenic bladder patients, has attracted much attention (51). The goal of developing a total bladder replacement however, is complicated by the fact that there is no afferent and efferent neural connection to the tissue engineered bladder. Therefore, there would not be the normal sensation of fullness (afferent signaling) nor contraction (efferent signaling) of the tissue engineered bladder. A more realistic goal is the development of a tissue engineered ileal conduit, where afferent/efferent signaling would not be required. This neoconduit would spare the use of native ileum. This technology is being currently developed by Tengion as the Neo-Urinary Conduit™ (www.tengion.com). It involves the removal of autologous fat from the patient which is processed in the laboratory so that adipose stem cells differentiate into urothelial and smooth muscle cells on a biodegradable scaffold.

Stem cells and tissue engineering continue to fascinate both the scientific community and public. It remains to be seen whether these technologies will be successfully implemented in urovesicology. Tissue engineering and stem cells approach problems in urovesicology from a different perspective in that knowledge of symptoms pathophysiology is not as important. Because these technologies are designed to augment or replace normal function of the bladder or urethra, the pursuit of why the bladder or urethra does not properly function becomes less critical. However, a close collaboration between tissue engineers/stem cell biologists with the physiologists could result in not just biologically compatible tissue, but tissue with true function.

Future of urovesicology from the metabolic syndrome level

Epidemiologic studies have found strong associations between urovesicologic symptoms and metabolic syndrome (insulin resistance, dyslipidemia, central obesity and hypertension) in men (52,53). More recently, similar associations were described in women (54). To strengthen these associations, researchers have found that weight loss decreased urovesicologic symptoms in both genders (55,56). However, a study on Chinese male population did not find significant associations between uroveiscologic symptoms with metabolic syndrome (57).

The cause of metabolic syndrome is multifactorial. Several theories exist of how metabolic syndrome relate to urovesicologic symptoms. One possibility is the increased autonomic activity seen in metabolic syndrome. Spontaneously hypertensive rats (SHR), due to increased autonomic activity from noradrenergic hyperinnervation, have bladder overactivity (58), thereby providing a proof-of-concept link between hyperautonomic activity and bladder overactivity. This link was studied and confirmed in a large study of men with urovesicologic symptoms (59). Other potential causal links include the pro-inflammatory state in metabolic syndrome and findings of inflammation in prostate of men with urovesicologic symptoms (60,61). The molecular link between metabolic syndrome and BPH may be PPARγ (peroxisome proliferator-activated receptor gamma or glitazone receptor) (62). PPARγ regulates inflammation and insulin resistance and thus sits at the crossroads between these two conditions, thereby potentially regulating both of these processes. These and other studies in the literature are starting to provide a picture that some of the urovesicologic symptoms may be part of a systemic disease rather than a primary lower urinary tract disease. Since a treatment directed at the metabolic syndrome (weight loss) resulted in lessening of urovesicologic symptoms, some could argue that addressing the systemic issue first, before treating the urovesicologic issues, could be a better strategy. However, it is likely that combination treatments for both conditions will be required in some patients. Also, more research into the causal links could potentially unlock novel targets that could treat both conditions.

Conclusions

Diagnosis and treatment of urovesicologic symptoms are imperfect. A primary reason is a lack of mechanistic understanding of why these symptoms occur and therefore, a lack of targeted treatments. A broad based research approach utilizing knowledge and technologies from other disciplines will help advance the field of urovesicology more quickly towards a better understanding of pathophysiology. Collaboration with researchers in other disciplines will accelerate discoveries resulting in a higher translational impact. The ultimate goal is to bring effective treatments to the many who suffer from urovesicologic symptoms. The future for urovesicology looks brighter than ever.

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Footnote

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