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REVIEW

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Developing new ways to assess neural control of pelvic organ function in spinal conditions: ICI-RS 2023

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Abstract

Objectives: Several central nervous system (CNS) centers affect muscle groups of the lower urinary tract (LUT) and anorectal tract (ART) via autonomic and somatic pathways, working in different modes (storage or expulsion). Hence spinal cord dysfunction can affect the LUT and ART by several possible mechanisms.

Methods: This review reports the discussions of a workshop at the 2023 meeting of the International Consultation on Incontinence Research Society, which reviewed uncertainties and research priorities of spinal dysfunction.

Results: Discussion focussed on the levator ani nerve, mechanisms underpinning sensory function and sensation, functional imaging, dyssynergia, and experimental models. The following key research questions were identified. (1) Clinically, how can we evaluate the levator ani muscle to support assessment and identify prognosis for effective treatment selection? (2) How can we reliably measure levator ani tone? (3) How can we evaluate sensory information and sensation for the LUT and the ART? (4) What is the role of functional CNS imaging in development of scientific insights and clinical evaluation? (5) What is the relationship of detrusor sphincter dyssynergia to renal failure?

Conclusions: Spinal cord dysfunction can fundamentally disrupt LUT and ART function, with considerable clinical impact. The evaluation needs to reflect the full scope of potential problems, and new clinical and diagnostic approaches are needed, for prognosis and treatment. The preclinical science evaluating spinal cord function in both LUT and ART storage and elimination remains a major priority, even though it is a challenging experimental context. Without this underpinning evidence, development of new clinical evidence may be held back.

KEYWORDS

anorectal, incontinence, lower urinary tract, neurogenic, pelvic floor dysfunction, spinal cord injury

1 | INTRODUCTION

Neural input to the lower urinary tract (LUT) and the anorectal tract (ART) coordinates several muscle groups to prevent content being expelled for the majority of the time, and to ensure that when expulsion does take place, it is in a suitable context. The peripheral nerves to the LUT and ART are carried in the parasympathetic and sympathetic divisions of the autonomic nervous system, and the ART additionally is regulated by the enteric nervous system. The somatic nervous system is also important, notably via the pudendal and levator ani nerves, which supply the LUT and ART outlets, and also the levator ani muscle (LAM). The relevant motor neurones are located in the spinal cord, predominantly the sacral part (LAM, the detrusor and Onuf's nucleus supplying the sphincters), though the thoracolumbar spinal cord contains the sympathetic nucleus (male bladder neck, and detrusor storage regulation).

Higher central nervous system (CNS) centers provide vital input which descends through the spinal cord to ensure muscle function is appropriately integrated and regulated. They also serve as the relay for ascending sensory information to the cerebrum, the level at which subconscious sensory information becomes consciously perceived as a sensation. Key reflexes integrate sensory and motor activity and underpin functions such as guarding, voiding, and male genitourinary function (emission and ejaculation).

The range of contributing centers and pathways, with autonomic and somatic control of several muscle groups working in different modes (storage or expulsion) means that spinal cord dysfunction can affect the LUT and ART by several possible mechanisms. Most obviously, one or more of the spinal cord centers regulating the muscles could be impaired, leading to reduced or absent muscle contraction in the affected distribution. Lesions elsewhere may increase muscle tone. Alternatively, sensory information might be disrupted, either by interrupting the sensory pathway from delivering information to the spinal cord, or by impeding pathways by which the information feeds through to the cerebrum.

This paper reports the discussions of a workshop at the 2023 meeting of the International Consultation on Incontinence Research Society, which reviewed uncertainties and research priorities of spinal dysfunction for the LUT and ART.

2 | MOTOR CONTROL

While the motor nerve supply delivered by the autonomic divisions and by the pudendal nerve is relatively well understood,[1] the levator ani nerve (LAN) is little researched. It is separate from the pudendal nerve and potentially provides a substantial proportion of the motor supply to the LAM.[2] There is limited research investigating the normal course and variation of the LAN pathway to the LAM.[3,4] Without standard clinical ways to assess normal variation and relative contribution of the LAN pathway, functional assessment of spinal cord injuries, lesions, or trauma on LAM and pelvic organ function, is incomplete. Indeed, this applies to full pelvic floor assessment of any urological, gynecological, or colorectal patient.

This can be exemplified by clinical evaluation of LAM in terms of over-activity and increased muscle tone, which is a problem relevant in many areas of pelvic floor dysfunction. Over-active LAM is the increase in muscle tension resulting from pain, stress, trauma, or weakness, which can be positively influenced by pelvic floor physiotherapy.[5–7] In comparison, hypertonic or nonrelaxing LAM occurs as a result of increased excitability or inflammation of the peripheral nerves, or as a result of chronic stress or trauma.[8]

In clinical practice, diagnosing over-activity or hypertonicity of the LAM is affected by the subjectivity of observation and palpation,[9–11] such that accurately differentiating between over-activity and hypertonicity is unreliable—noting that both reflect increased muscle activity. When functionally assessing LAM strength using either the PERFECT score[12] or the Oxford grading scale, there is inter- and intrarater variability.[13] Ultrasound scanning is unable to identify tonal changes.[14,15] There may be an argument for the use of electromyography (EMG) with dynamometry to investigate neural activity of the LAN and change to LAM tone.[8,16,17] Nonetheless, both patient groups typically receive conservative treatment through physiotherapy. Unfortunately, hypertonic LAM are generally nonresponsive to physiotherapy intervention,[18] and if individuals do not respond to LAM physiotherapy, they are considered for more medical interventions, for example, botulinum toxin injection.[19] Hence, there is a risk of futile intervention and delay in patient care. Accordingly, further exploration is needed both for understanding the contribution of the LAN, and to establish a reliable and objective measure for grading LAM strength.

3 | BLADDER AND BOWEL AFFERENT PATHWAYS

Sensory information sent to the spinal cord from the ART and LUT is complex, with uncertainty regarding what information is encoded in the afferent nerve traffic, and how it is transduced. Two key aspects of LUT afferent

information report state of bladder filling, and presence of urine flow in the urethra.[20] Both structures (bladder and urethra) additionally can report noxious stimuli. The anorectal receptors report pressure and stretch.[21]

The afferent signaling from the pelvic viscera to the spinal cord runs in all three peripheral nerve groups innervating the organs: the hypogastric (sympathetic) nerve toward spinal cord level T10-L1, the pelvic (parasympathetic) nerve toward S2–S4, and the somatic pudendal nerve at S2–S5 (Table 1).

In the spinal cord, sensory information is transported through different pathways.[23] The dorsal columns convey sensory information relevant to sensation of filling and desire to void for the LUT. For the ART, they convey information related to fullness, desire to defecate, maximum tolerated volume, and fecal content. They also carry sensory information from the pelvic floor. The lateral spinothalamic tracts carry urgency, pain, touch, temperature, and electrosensation (the ability to perceive electrical stimuli) for the LUT, and similar sensations for the anorectum, perhaps also with an immune and microbial element. The anterior spinothalamic tracts carry information about contraction for both organs.

For the LUT, spinal cord injury generally impairs LUT sensation, however, in can be preserved in many, even with a severe lesion.[24] Electrosensation in different parts of the organs may be related to a different sensory innervation.[23] For the ART, sensation reported during anorectal balloon inflation and electrosensation are equivalent modalities. Here, disorder in sensory testing has been described in different neurologic disturbances such as spinal cord injury, dementia, postpelvic radiation, after surgical resection for rectal cancer and diabetes.[23]

4 | HIGHER BRAIN CENTERS

The afferents from the bladder facilitate ascending input signals that convey to the periaqueductal gray (PAG). Different parts of the brainstem and brain receive and distribute sensory information; bladder filling and rectal distention activate regions of the brain involved in sensory processing in healthy adults.[25] Crucially, the prefrontal cortex (PFC) is responsible for controlling the regulation of the LUT and ART within the totality of an individual's complex cognitive and social behaviors.[26] The medial and lateral prefrontal areas are involved in making the decision whether micturition should take place. It is believed that, for voiding to occur, the PMC requires both an excitatory signal from the PAG and a "safe" signal from the hypothalamus. Voiding is ultimately controlled by the external urethral sphincter (EUS), which is normally constricted but relaxes at the start of micturition by descending input from the brainstem. Sphincter relaxation, which is normally under voluntary control, is disinhibited when a lesion involves the frontal lobe and hypothalamus.[27] Using a retrovirus-based retrograde trans-synaptic tracing strategy, morphological results showed that urination-related PAG neurons receive dense inputs from multiple urination-related higher brain areas, such as the medial preoptic area, medial PFC, and lateral hypothalamus.[28]

The function of the ART is regulated by the medulla oblongata and the sacral spinal cord. Small intestine and ascending colon are innervated by the vagus nerves originating in the medulla. Both the sacral cord and the vagus nuclei receive projecting fibers from Barrington's nucleus (the pontine micturition/defecation center). The lower bowel (descending colon, sigmoid colon, and rectum) share sacral innervation with the LUT, modulated by the higher brain structures including the frontal lobe, the hypothalamus, and the basal ganglia.[29] Most areas activated in functional neuroimaging by bowel distention[30] strikingly overlap the area activated by bladder distention.

5 | ADVANCED FUNCTION AND IMAGING MODALITIES

Modern tests to evaluate neuronal control of LUT function may include neurophysiological and neuroimaging (i.e., flow/metabolic) brain-mapping

TABLE 1 The different sensations and the peripheral nerves through which they run.

	Pelvic	Hypogastric	Pudendal
Sensation of filling/fullness	Yes	Probably	No
Desire to void/defecate	Yes	Probably	No
Strong desire to void/maximum tolerated rectal volume	Possibly	Probably not	Yes
Pain—bladder	Yes	Yes	No
Pain—urethra/anorectum	Probably	Probably not	Yes

Source: Adapted from Morrison.[22]

techniques.[31] This network analysis can help explore structural-functional mechanisms and etiological relationships that link connectivity abnormalities to neuropathological diseases. Another approach to investigate the central circuits may involve functional near-infrared spectroscopy which has the benefits of noninvasive, portable, and optic-based testing, and avoids excessive restriction of physical mobility.[32]

Functional neuroimaging has emerged as a pivotal tool in elucidating CNS control of many functions. Functional magnetic resonance imaging (fMRI) enables noninvasive assessment of activity patterns during various phases of LUT control. The recent emergence of ultrahigh field scanners improves the signal-to-noise ratio, enabling individualized analysis, and facilitates high-resolution assessment of small CNS nuclei that were previously inaccessible.[33] Recent advances in neuroimaging suggest that functional measurement of activity in the sacral spinal cord may be feasible, which would enable direct assessment of activity in Onuf's nucleus and other relevant spinal nuclei.[34]

Neuroimaging studies have unraveled functional and structural differences in the CNS between healthy adults and patients with LUT dysfunction, such as idiopathic overactive bladder syndrome (OAB).[35,36] This potentially can fine-tune diagnostic procedures, identify predictors of outcome, and enable objective assessment of responses to therapeutic interventions. Evaluation of CNS activity during manipulation of bladder sensations (using automated bladder filling via a catheter) in spinal cord injury (SCI) patients has indicated that CNS processes associated with bladder sensations are, to some extent, present in brain areas associated with vagal afferents in patients with complete lesions between C7 and T5.[37] Furthermore, in SCI patients with incomplete lesions between C5 and T11, neuroimaging during a bladder filling protocol, with simultaneous pudendal nerve stimulation (acute and long-term), enabled identification of changes in CNS activity in brain areas associated with LUT sensory processing (e.g., the insula) in conjunction with the clinical effect of pudendal nerve stimulation.[38] The use of advanced neuroimaging methods such as resting-state assessment and identification of functional connectivity,[39] in particular in autonomic brain-stem/mid-brain areas (notably the PAG, Barrington's nucleus/the PMC), are essential to improve our understanding of (mal) adaptive changes in CNS control.

Although neuroimaging advancements are promising, it remains challenging to design experiments that reliably elicit sensations (let alone symptoms) in the scanner. An obvious limitation is the necessity of the supine position in fMRI experiments, which often limits the extent to which patients exhibit detrusor overactivity and experience adequate LUT sensations. Furthermore, the relatively slow nature of natural diuresis limits repetition of bladder filling within a scanning session. Hence, researchers often rely on automated bladder filling, with the associated risk of sensory artefacts, to obtain the multiple measurements needed to conduct robust analyses. Differentiating CNS activity directly resulting from LUT stimuli versus CNS-evoked sensations is a key challenge in using this technique. Fluid infusion or withdrawal to vary the bladder volume can influence a recognized trigger of LUT sensory processing during a scan,[40] so identification of different patterns of activity on imaging could suggest relevant pathways carrying the information. An interesting adaptation is to elicit CNS-evoked sensations by presenting visual psychological stimuli,[41] for example, images of "personal urgency triggers" to elicit OAB symptoms during a scan.

6 | URODYNAMIC (UDS) ASSESSMENT AND ALTERNATIVES

UDS is the principal means to assess LUT function in patients with spinal cord dysfunction. It is the established method to objectively evaluate intravesical pressure. Combined with radiological imaging (videourodynamics; VUDS), it enables identification of key risk factors of upper urinary tract damage and renal failure, notably vesicoureteric reflux (VUR), detrusor bladder neck dyssynergia (DBND), detrusor sphincter dyssynergia (DSD), and potentially sustained detrusor overactivity (DO) and/or low bladder compliance.[42–45]

The specific features of neurogenic LUT dysfunction depend on the level of the deficit.[46,47] In general, complete sacral or infrasacral lesions lead to an acontractile detrusor (necessitating increases in intraabdominal pressure to enable bladder emptying, that is, Valsalva straining) and intrinsic sphincter deficiency (leading to stress urinary incontinence. Nonetheless, some patients may have residual sphincter tome, that is, sufficient to prevent bladder emptying. In suprasacral lesions, 70%–80% of the patients will experience neurogenic DO, sometimes associated with DSD.[48] Other specific UDS patterns in SCI leading to high intravesical pressure are associated with upper urinary tract morbidity.

DSD is a detrusor contraction concurrent with an involuntary contraction of the urethral and/or periurethral striated muscle.[49] There is a perceived relationship between DSD and risk of deterioration in upper urinary tract function. Nonetheless, DSD can be categorized,[50,51] raising the possibility of a more severe phenotype which causes the greater renal risk, and

conversely a low-risk DSD. The parameters underpinning this are likely to be influenced by absolute pressure, duration of increased pressure and VUR, but the thresholds which place someone at greater risk are not known. Unfortunately, this would be difficult to study, since VUDS is only a short duration test under artificial conditions. Even ambulatory UDS, with a longer duration and greater mobility (within the limits of the patient's condition), can only provide a fragmentary insight into DSD. Nevertheless, high storage pressures are a red flag mandating particularly careful clinical and diagnostic assessment.

DSD is related to an upper motor neuron suprasacral lesion (with preserved sacral centers), leading to impaired control, segmental spinal reflex (DO), and impaired coordination between detrusor and EUS.[52] One key clinical element is the recognition of the basis of onset. DSD in complete SCI is entirely involuntary; typically, the patient experiences DO, with DSD evident in some of the DO episodes. In contrast, some people with an incomplete spinal cord lesion (notably in MS) may have the facility to initiate voiding voluntarily, but the spinal cord dysfunction affects the normal synergy of outlet relaxation, so that sphincter relaxation may be impaired. Hence the sphincter closure is a feature of their voiding—akin to dysfunctional voiding, but neurologically driven over behavioral. This might be termed dyssynergic voiding when the person decides to void. Whereas DSD occurs when voiding is involuntary and controlled by reflex actions outwith the voluntary control of the person. For all these circumstances, the specific pathways of the reflexes are poorly understood.

DSD can be diagnosed on UDS by the characteristic hydrodynamic pattern that flow occurs when the pressure drops (since pressure is high when the outlet is contracted and preventing flow). Observing this pattern in the relevant clinical context (suprasacral spinal cord dysfunction) can be sufficient to diagnose DSD. Use of EMG may also suggest the active contraction of the sphincter,[47] though most clinical evaluation uses pelvic floor EMG, rather than recording directly from the urethral sphincter. VUDS can give a visual indicator, which can help distinguish DSD from DBND.[53] The latter reflects concomitant uncoordinated bladder and bladder neck contractions resulting in bladder neck functional obstruction.[47] Using VUDS, DBND is defined as a narrow bladder neck during voluntary or involuntary detrusor contraction.[54]

The link between DBND and a specific neurological level of injury remains unclear. In the series of Wang et al., DBND was associated with the level of injury (most common in cervical and high thoracic lesions) rather than the completeness of the injury,[54] contrasting with the observations reported by Schurch and colleagues.[47] For the ART, less is known about anorectal manometry in spinal cord dysfunction; attempts to categorize on the basis of rectal pressure and sphincter tone in response to rectal distention have been described,[55] but the area has received comparatively limited attention.

7 | EXPERIMENTAL CONTEXT

The complex pathology of spinal cord dysfunction is not static but evolves over time. Hence, it is not amenable to the traditional, "one drug fits all," treatment approach. Furthermore, the circumstances of evaluation for therapeutic interventions is hugely restricted. Clearly ethical constraints apply to human testing, but the difficulty of the spinal cord as an experimental target (notably complexity and access), plus the homeostatic disruption due to the trauma, necessitate animal models for fundamental insights.

In the LUT, the potential of this type of research can be exemplified by work on the therapeutic potential of three small molecule drugs to promote functional recovery after severe (75 kDy) mid-thoracic T8–T9 spinal cord contusion (SCC) in mice. LM11A-31, a p75 neurotrophin receptor modulator, counters the activation of cell death pathways in early stages of SCC. LM22B-10, targeting tropomyosin-related kinase receptors, is able to promote neural survival, growth, and remodeling. Cinaciguat, a soluble guanylate cyclase (sGC) activator, enhances reperfusion/oxygenation to aid in the repair of spinal cord lesions. It also inhibits/reverses fibrosis to improve mobility and bladder function.[56] Such work can characterize mechanisms of action and therapeutic windows for the underlying lesion. Potentially, there is an additional therapeutic opportunity in ameliorating abnormal reflex activity such as DSD and neurogenic DO. LM11A-31 and cinaciguat have passed phase I and IIa clinical trials and have a significant potential for accelerated clinical testing in patients with spinal cord-related LUTD. Experimental observations support the mechanisms of action and therapeutic windows for these three small molecule drugs in the treatment of the SCC-induced lesions, DSD, DO, and bladder fibrosis, to help establish the scientific rationale for a multipronged treatment approach to achieve measurable improvement in motor and LUT dysfunction at central and peripheral sites. Hence, this sort of research indicates that detailed investigation and moderation of spinal cord dysfunction can be studied, once constraints of the clinical context do not apply.

8 | RESEARCH DIRECTIONS

1. *Question*. Clinically, how can we evaluate the LAM to support assessment and identify prognosis for effective treatment selection?

   Potential answer. This may necessitate adaptations to the clinical history and examination, to identify the normal variability in the LAN pathway and its contribution to LAM motor function.
2. *Question*. How can we reliably measure LAM tone?

   Potential answer. A clinically feasible way to measure LAM tone may necessitate development of an affordable and reliable device.
3. *Question*. How can we evaluate sensory information and sensation for the LUT and the ART?

   Potential answer. This has been a long-standing scientific challenge with only indirect means still available, but it remains a high priority.
4. *Question*. What is the role of functional CNS imaging in development of scientific insights and clinical evaluation?

   Potential answer. Functional imaging has made initial progress, but consensus on the optimal trade-off between imaging and protocol is needed for advancement in understanding the central CNS control and whether the techniques are applicable for clinical use.
5. *Question*. What is the relationship of DSD to renal failure?

   Potential answer. Relevant classification of DSD for clinical risk using longitudinal epidemiological studies is still needed; even though protection of renal function is a priority in neurological LUT dysfunction, over-treatment needs to be avoided.

Finally, the preclinical science evaluating spinal cord function in both LUT and ART storage and elimination remains a major priority, even though it is a challenging experimental context. Without this underpinning evidence, development of new clinical evidence may be held back.

9 | CONCLUSIONS

Spinal cord dysfunction can fundamentally disrupt LUT and ART function, with considerable clinical impact. The evaluation needs to reflect the full scope of potential problems, and new clinical and diagnostic approaches are needed, for prognosis and treatment. The preclinical science evaluating spinal cord function in both LUT and ART storage and elimination remains a major priority, even though it is a challenging experimental context.

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CONFLICT OF INTEREST STATEMENT

J. B. G. Meden-Inmed Sp. Z.o.o. M. J. D. Astellas fees. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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