The Other Bladder Syndrome: Underactive Bladder

Minoru Miyazato, MD, PhD,[1,2] Naoki Yoshimura, MD, PhD,[2,3] Michael B. Chancellor, MD[4]
[1]Department of Urology, Graduate School of Medicine, University of the Ryukyus, Nishihara, Okinawa, Japan; [2]Department of Urology, University of Pittsburgh School of Medicine, Pittsburgh, PA; [3]Department of Pharmacology & Chemical Biology, University of Pittsburgh School of Medicine, Pittsburgh, PA; [4]Department of Urology, William Beaumont Hospital, Royal Oak, MI

Detrusor underactivity, or underactive bladder (UAB), is defined as a contraction of reduced strength and/or duration resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span. UAB can be observed in many neurologic conditions and myogenic failure. Diabetic cystopathy is the most important and inevitable disease developing from UAB, and can occur silently and early in the disease course. Careful neurologic and urodynamic examinations are necessary for the diagnosis of UAB. Proper management is focused on prevention of upper tract damage, avoidance of overdistension, and reduction of residual urine. Scheduled voiding, double voiding, α_1-blockers, and intermittent self-catheterization are the typical conservative treatment options. Sacral nerve stimulation may be an effective treatment option for UAB. New concepts such as stem cell therapy and neurotrophic gene therapy are being explored. Other new agents for UAB that act on prostaglandin E_2 and EP_2 receptors are currently under development. The pharmaceutical and biotechnology industries that have a pipeline in urology and women's health may want to consider UAB as a potential target condition. Scientific counsel and review of the current pharmaceutical portfolio may uncover agents, including those in other therapeutic fields, that may benefit the management of UAB.

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KEY WORDS

Detrusor overactivity • Diabetic cystopathy • Overactive bladder • Underactive bladder

We are all familiar with overactive bladder (OAB) syndrome. OAB is common and there are several antimuscarinic drugs available globally for its treatment. In addition, neuromodulation and botulinum toxin are also minimally invasive treatment options. Yet, there is an inverse condition that is also important but remains below the radar of most experts and the public. This article reviews underactive bladder (UAB), the opposite of OAB.

Urologists treat patients with UAB but there is no consensus for its definition. *Detrusor underactivity*, *urinary retention*, *high residual urine*, and *incomplete bladder emptying* have been used. Detrusor underactivity is defined by the International Continence Society as a contraction of reduced strength and/or duration resulting in prolonged or incomplete emptying of the bladder, but has received only minimal attention.[1] Patients with UAB have a diminished sense of when the bladder is full and are not able to contract the muscles sufficiently, resulting in incomplete bladder emptying.

Some of the established causes of UAB include neurogenic, myogenic, aging, and medication side effects. Symptoms of UAB overlap those of OAB syndrome; some common symptoms include urgency, frequency, nocturia, and incontinence that may be overflow, urge, and/or stress. Some symptoms more commonly associated with UAB include hesitancy, sensation of incomplete emptying, straining to void, and recurrent infections.

Contributing Factors

OAB may, over time, lead to the development of UAB (Table 1). Recent research has demonstrated that the bladder wall thickens with OAB[2,3] and there is a rise in urine nerve growth factor (NGF) levels.[4] Therefore, OAB may involve structural changes that may eventually lead to alteration of muscle and connective tissue structure and function that can result in impaired contractility. It is therefore possible that chronic OAB leads to detrusor hyperreflexia/impaired contractility that progresses to UAB? If so, then it is possible that early OAB therapy may prevent the development of UAB by as much as 20 years?

UAB is usually observed when the following mechanisms are damaged[5]:

- Bladder peripheral afferent pathways
- Bladder peripheral efferent pathways
- Lumbosacral spinal cord (spinal micturition center)
- Myogenic failure

Diabetes Mellitus (Diabetic Cystopathy)

Bladder dysfunction associated with the complication of diabetes mellitus (DM), classically referred to as diabetic cystopathy, has been described as impaired sensation of bladder fullness, increased bladder capacity, reduced bladder contractility, and increased residual urine.[6-8]

These classic symptoms are not always observed in the patient with DM and symptom presentation varies. Moreover, common concomitant diseases such as urinary tract infection, benign prostatic hyperplasia, and stress urinary incontinence may obscure underlying diabetic cystopathy. Therefore, it is important to discern the major factor from the complex presentation of symptoms in an individual patient. It has also been reported that diabetic cystopathy can occur silently and early in the course of DM.[9] In those cases, it is typical that bladder dysfunction induced by DM is only found with careful questioning and/or urodynamic testing.

TABLE 1

Causes of Underactive Bladder

Diabetes mellitus (diabetic cystopathy)
Bladder outlet obstruction
Aging
Neurologic disorders
Acute cerebrovascular accidents
Multiple sclerosis
Parkinson disease
Injury to the spinal cord, cauda equina, and pelvic plexus
Pelvic surgery
Pelvic and sacral fractures
Herniated disc
Lesions of the pudendal nerve
Infectious neurologic problems
AIDS
Neurosyphilis (tabes dorsalis)
Herpes zoster and herpes simplex
Guillain-Barré syndrome

The sex and age of patients is not related to prevalence, although the duration of DM is related to the prevalence of diabetic cystopathy.[9]

Pathogenesis of Diabetic Cystopathy. Pathophysiology of diabetic cystopathy has multifocal aspects. Traditionally, diabetic cystopathy was thought to result from polyneuropathy that predominantly affects sensory and autonomic nerve fibers.[10,11] Some aspects of the proposed pathogenesis include altered metabolism of glucose, ischemia, superoxide-induced free-radical formation, impaired axonal transport, and metabolic derangement of the Schwann cells.[12,13] In addition to neuronal changes, many recent studies suggest that diabetic cystopathy can result from an alteration in the physiology of the detrusor smooth muscle cell or urothelial dysfunction.[13]

The sex and age of patients is not related to prevalence, although the duration of DM is related to the prevalence of diabetic cystopathy.

Detrusor smooth muscle function has shown altered physiology in streptozocin (STZ) or alloxan-induced DM in animal models. Major physiologic alterations are changes in sensitivity and contractile forces. Although there is some controversy regarding the response to muscarinic agonists, most agree on the increased response of DM bladder strip to electrical field stimulation.[14,15] These changes are suggested to reflect increased calcium channel activity and enhanced calcium sensitivity.[15] Changolkar and colleagues[16] reported that DM induced a decrease of detrusor smooth muscle contractility and an increase of oxidative stress factors, an increase in lipid peroxidase/sorbitol, and concomitant overexpression of aldose reductase/polyol pathway activation. The same group also reported increased expression of thin filament proteins: calponin, tropomyosin, and caldesmon in DM rabbit bladder, which might alter the contractile and cytoskeletal structure.[17]

The changes of tissue neurotrophic factors such as NGF have been researched as a convincing pathogenesis of diabetic neuropathy.[18-23] The changes of another neurotrophic factor, neurotrophin-3, have also been reported.[24-26] It is promising for future treatment strategies that changes in tissue neurotrophic factor could play a critical role in inducing diabetic cystopathy.

Recent studies have shown that urothelium is not a passive barrier but can play an active role in bladder physiology.[13] The urothelium can release many mediators including adenosine triphosphate (ATP), nitric oxide (NO), and prostanoid.[27,28] Pinna and colleagues[29] reported that, in isolated urothelial layer preparations from STZ-DM rats, the amount of endogenous prostaglandin E_2 (PGE_2) and $F_{2\alpha}$ was higher than the preparations from normal rats. ATP and bradykinin significantly increased the endogenous release of PGE_2 and $F_{2\alpha}$ from the urothelium when compared with basal release level. This time-dependent increase was higher in diabetic tissue than control tissue. Prostaglandins may increase the sensitivity of DM bladder tissue to contractile stimuli.

NO synthase (NOS) and reactive nitrogen species formation are also changed during DM-related bladder remodeling. Poladia and Bauer[30] reported that endothelial NOS is significantly upregulated in the lamina propria, neuronal NOS in the urothelium, lamina propria, and smooth muscle, whereas inducible NOS is upregulated only in the urothelium. They suggested that impaired NO control is an early event leading to increased oxidative stress and proteasomal activation in pathogenesis of diabetic cystopathy.

Bladder Outlet Obstruction

Obstruction to the urinary outflow tract can result in chronic changes within the bladder wall.[31] Prostatic enlargement is a very frequent cause of obstruction due to hyperplasia or, less frequently, prostate cancer. Severe vaginal prolapse can also lead to obstructed voiding. In contrast, in a minimum 10-year urodynamic follow-up in men with bladder outlet obstruction (BOO), Al-Hayek and colleagues[32] reported that detrusor contractility does not decline in the long term.

Aging

Detrusor hyperactivity with impaired contractility is a frustrating diagnosis for clinicians and patients because current treatment options are largely palliative.[33] Age-related symptoms such as urinary retention, urinary hesitancy, and incontinence have been attributed to UAB.[34-36] Elbadawi and colleagues[37] described qualitative changes in detrusor muscle associated with advanced age and UAB. Human urodynamic data also suggest a loss of bladder contractility and voiding efficiency with age.[38,39] In contrast, Ameda and associates[40] found no significant correlation between age and impaired detrusor contractility, as defined by continuous occlusion test or unsustained detrusor contraction during voiding.

Aging and Bladder Afferents. In animal studies, impaired bladder function is evidenced by

increased volume and pressure thresholds for voiding and diminished response to intravesical capsaicin instillation.[41,42] In addition, aged rats exhibit reduced sensitivity of pelvic nerve afferents in response to increased bladder volume, but not pressure, and a reduction in the maximal bladder pressure generated during pelvic nerve stimulation.[43] A significant linear reduction in the amount of acetylcholinesterase-positive nerve was observed with increasing age in the human bladder,[44] suggesting reduced parasympathetic innervation. It is also shown that expression of neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P in lumbosacral dorsal root ganglion neurons decreases with age,[45] and there is a marked reduction in the density of pituitary adenylate cyclise activating polypeptide innervation of the subepithelial plexus and of the muscle layer of the bladder base as well as slight reductions in CGRP and substance P innervation of the muscle layer in old rats.[46]

In humans, functional magnetic resonance imaging in asymptomatic patients demonstrates age-related diminished response to bladder filling in the insula, an area of the brain responsible for mapping visceral sensations.[47] Yoshida and colleagues[48] showed nonneuronal acetylcholine release in response to tension in bladder strips increases with age, suggesting that bladder afferent mechanisms change with age.

Aging and Bladder Morphology. Age-induced morphologic changes include a decrease in the ratio of detrusor muscle to collagen, changes in collagen and muscle quantity, and a decrease in axonal content.[44] An age-related decrease in M3 muscarinic receptor concentration may diminish potential sensitivity of micromotional activity to cholinergic neurotransmitter.[49]

Neurological Disorders

Acute Cerebrovascular Accidents. Cerebrovascular accident (CVA) is a serious neurologic event and it can cause temporary or permanent voiding dysfunction to the victims. It is generally accepted that the most common urodynamic finding in CVA patients is detrusor overactivity. However, Burney and colleagues[50] reported urodynamic evaluations in 60 CVA patients performed within 72 hours of the accident. In their series, 47% of patients had urinary retention, mainly due to areflexia detrusor (75%). Detrusor areflexia was found to be more common in hemorrhagic infarcts (85%) compared with only 10% with ischemic infarct. Although most cortical and internal capsular lesions resulted in detrusor overactivity, all cerebellar infarcts resulted in detrusor areflexia.

Parkinson Disease

Parkinson disease is a degenerative disorder of the CNS characterized by muscle rigidity, tremor, and a slow physical movement. These symptoms result from decreased stimulation of the motor cortex by the basal ganglia, usually caused by the insufficient formation and action of dopamine, which is produced in the dopaminergic neurons of the brain. The most common finding in urodynamic studies is detrusor overactivity, which reflects the CNS involvement in this condition. However, UAB has also been reported in up to 16% of patients reviewed in these studies.[52]

Injury to the Spinal Cord, Cauda Equina, and Pelvic Plexus

Any trauma to the spinal cord, such as blunt, degenerative, developmental, vascular, infectious, traumatic, and idiopathic injury, can cause voiding dysfunction. Injury to the cauda equina or peripheral sacral nerves can have a devastating effect on bladder and urethral sphincter function. The resulting urinary dysfunction can be a major cause of morbidity in these cases. Lumbosacral spinal cord injury and herniated intervertebral disc are the two most common etiologic factors.[53,54] Other etiologic causes include lumbar spinal stenosis, myelodysplasia, spinal arachnoiditis, arteriovenous malformations, and primary or metastatic tumors of the lumbar spine. It is also a rare complication of regional anesthesia.

Injury to the pelvic plexus is uncommon. It is usually iatrogenic, most often occurring after major

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Multiple Sclerosis

Multiple sclerosis (MS) is a chronic disease with focal demyelinization of the central nervous system (CNS) at various levels, causing a wide spectrum of neurologic manifestation. Urologic problems are reported in up to 90% of patients and represent the most troublesome and socially disabling feature of the disease course.[51] Storage symptoms such as frequency, urgency, and urge incontinence are more common, but voiding symptoms such as weak stream, straining, and large residual urine are also common manifestations in patients with MS.

abdominal and pelvic surgery such as abdominoperineal resection or radical hysterectomy. Sometimes the problem may result from a pelvic fracture, or the trauma may be intentional (eg, transvesical phenol injection) to abolish neurogenic detrusor overactivity in patients who have failed standard treatment regimens.

Infectious Neurologic Problems

AIDS. AIDS is commonly associated with neurologic dysfunction. Neurologic involvement occurs in as many as 40% of patients with AIDS.[55] Urodynamic evaluation in a series of 18 AIDS patients with voiding symptoms revealed neurogenic bladder in 11 patients.[56] Urinary retention was the most common presenting symptom, and was seen in 6 of the 11 patients (55%); urodynamic study revealed UAB in 36% of patients, OAB in 27%, and BOO in 18%.

Neurosyphilis (Tabes Dorsalis). Neurosyphilis has long been recognized as a cause of central and peripheral nerve abnormalities. Voiding dysfunction related to neurosyphilis was common in the era before penicillin use. Hattori and associates[57] reported decreased bladder sensation in tabes dorsalis. The most common urodynamic finding in neurosyphilis is UAB.

Herpes Zoster and Herpes Simplex. Herpes zoster is an acute, painful mononeuropathy associated with a vesicular eruption in the distribution of the affected nerve. The viral activity is predominantly located in the dorsal root ganglia, or sensory ganglia of the cranial nerves. However, sacral nerve involvement may be associated with loss of bladder and anal sphincter control.[58] The early stages of lower urinary tract involvement with herpes are manifested as symptomatic detrusor instability with urinary frequency and urgency, but the latter stages include decreased sensation of filling and elevated residual urine or urinary retention.[59] On the positive side, the problem is only temporary and generally recovers spontaneously over several months.

Guillain-Barré Syndrome. Guillain-Barré syndrome, also known as postinfectious polyneuritis, is an acute symmetric ascending polyneuropathy occurring 1 to 4 weeks after an acute infection. The syndrome is characterized by rapidly progressive signs of motor weakness and paresthesias progressing from the lower to upper extremities. Urine retention may occur in the early stages and require bladder catheterization.[60] Long-term urological dysfunction is uncommon.

Diagnosis

Clinical Findings

Patients with known or suspected neurologic injury due to pelvic or sacral injury should have a careful physical examination. The integrity of the sacral dermatomes is tested by assessing perianal sensation, anal sphincter tone, and the bulbocavernosus reflex.

The type of resulting functional disturbance will depend on the nature and extent of nerve injury. Parasympathetic denervation causes UAB, whereas sympathetic damage will produce loss of proximal urethral pressure as a result of the compromised alpha adrenoceptor-mediated innervations to the smooth muscle fibers of the bladder neck and urethra.[61,62]

Many patients complain of straining to urinate, incontinence, and sensation of incomplete emptying. The urinary stream may be diminished and interrupted, as many of these patients rely on abdominal straining to urinate. On occasion, symptoms of voiding dysfunction may be the only initial clinical manifestation of a cauda equina lesion.[63] The varied and mixed symptomatologies emphasize the need for a complete neurourologic evaluation.

The physical examination may reveal a distended bladder, but the most characteristic features are elicited on careful neurologic examination. Sensory loss in the perineum or perianal area is associated with S2-S4 dermatomes. The extent of perineal anesthesia can be a useful predictive clinical index in patients with lumbar disc prolapse. If saddle anesthesia of the S2-S4 dermatomes continues after surgical laminectomy and decompression, the urinary bladder rarely recovers.[64] However, a unilateral or mild sensory disturbance indicates a better prognosis. Deep tendon reflexes in the lower extremities, clonus, and plantar responses, as well as the bulbocavernosus reflex, should be routinely evaluated.

In a series of patients with cauda equina injury of various etiologies, the bulbocavernosus reflex was absent or significantly diminished in 84% of cases, whereas the perineal sensation and muscle stretch reflexes were compromised in 77% of cases.[65] In addition, it was noted that reflex absence correlated well with perineal floor denervation.[66]

It is of interest that parasympathetic denervation itself may actually increase adrenergic activity by unmasking already existing α-receptors or inducing α-receptors. It has been demonstrated by histochemical fluorescence studies that the adrenergic nerve terminals of denervated human detrusors were thicker and denser than those of neurologically normal detrusors. A complete injury of the pelvic plexus disrupts the nerve supply to the bladder and the urethra, but most injuries are

incomplete. Because most ganglia lie close to or within the bladder wall and large numbers of postganglionic neurons remain intact, any denervation is followed by reinnervation,[67] so that some residual lower tract activity remains. Sensation may be preserved, but if it is lost, the resultant symptoms are usually urinary retention and overflow incontinence.

Peripheral sympathetic injury results in an open, nonfunctional bladder neck and proximal urethra. Although this could occur as an isolated injury, it typically occurs in association with partial detrusor denervation, but with preservation of sphincter function.[62] The combination of decreased compliance, open bladder neck, and fixed external sphincter resistance results in the paradoxical symptomatology of both leaking across the distal sphincter and the inability to empty the bladder. Under these circumstances, the optimal management is a combination of anticholinergics and intermittent catheterization.

Urodynamic Testing of UAB: Diabetic Cystopathy

In most typical cases of diabetic cystopathy, cystometry shows a long curve with lack of sensation, often until bladder capacity is reached, with a low detrusor pressure.[8,68,69] However, it has been reported that this classic type of underactive diabetic cystopathy is sometimes modified by concomitant lesions such as BOO or a history of cerebrovascular disease. For example, previous studies have reported an incidence of detrusor overactivity up to 50% to 60% when bladder function was examined in a select population of patients with DM who presented with positive lower urinary tract symptoms or a history of stroke.[70,71] BOO should also be considered as a differential diagnosis for detrusor overactivity in patients with diabetes.[68] BOO is documented by measuring a high or normal pressure in the presence of an impaired urinary flow rate. Some patients with both diabetic cystopathy and BOO exhibit detrusor overactivity and elevated detrusor pressure during low-flow voiding.

Previous studies have reported an incidence of detrusor overactivity up to 50% to 60% when bladder function was examined in a select population of patients with DM who presented with positive lower urinary tract symptoms or a history of stroke.

However, despite recent reports of a relatively high incidence of detrusor overactivity in symptomatic DM patients,[70] one should be aware that autonomic and sensory neuropathy with diminished bladder sensation and bladder contractility is the predominant urologic manifestation of diabetic cystopathy when unselected DM patients are examined.[6-8] Electromyography is usually normal but sometimes exhibits sphincter denervation and uninhibited sphincter relaxation. Uroflowmetry shows low peak flow and prolonged duration of flow associated with increased residual urine. Urethral pressure profiles have not been well studied or validated in diabetic cystopathy.[8,72]

Models

Better animal models need to be established to allow accurate testing of potential therapeutic candidates. Currently, obstruction, diabetes, denervation, hydrodistension, and segmental mechanical or therapy damage are of modest value (Table 2).

Diabetes

DM can be induced by a single intraperitoneal injection of STZ (65 mg/kg), as previously reported by Torimoto and colleagues.[73] Major physiologic alterations include changes in bladder afferents and contractile activity. Myocytes from the DM rat have shown increased depolarization to externally applied acetylcholine and decreased spontaneous activity, presumably related to altered

TABLE 2

Animal Models of Underactive Bladder

Model	Methods
Diabetes (rats, rabbit)	Intraperitoneal injection of streptozotocin
Aging (rats, mice)	Aging rats (12-24 mo)
Bladder outlet obstruction (rats)	Ting urethra near the bladder neck or in the posterior urethra
Hydrodistension (rats)	Overdistended bladder under pressure-guided
Pelvic nerve transaction (rats)	Bilateral pelvic nerve transaction
Cryoinjury of bladder (rats)	Cryoinjury of bladder using dry ice

purinergic transmission.[74] In STZ-DM rats, the decrease of tissue NGF levels in the bladder and bladder afferent pathways are associated with diabetic cystopathy.[75]

Aging

Chai and associates[41] demonstrated the utility of 24-month-old F344 male rats to study micturitional changes that result from aging. Aged rats voided less frequently and had a higher volume per void and higher micturitional threshold pressure than young rats. Intravesical capsaicin caused a lower pressure bladder response in the aged rats compared with the young rats, suggesting impaired bladder contractility in the elderly may be exacerbated by reduced sensory input. Lluel and colleagues[76] also reported impairment of the urethrovesical coordination in aging (24-month-old) male rats.

BOO

BOO can be created by ting urethra near the bladder neck in female rats or posterior urethra in male rats.[31] In a rat with BOO, residual urine volume is increased and bladder contractility is decreased. On histologic examination, thickening of the interstitial tissues in the bladder and infiltration of immune cells into the interstitium is observed.[31] Mori and colleagues[77] reported a decreased cellular membrane expression of gap junction protein (connexin-43) in the detrusor muscle in rats with BOO, suggesting the disruption of gap junctional intercellular communication.

Hydrodistension

Kim and associates reported a UAB model (ie, a pressure-guided distention model) that induces ischemia and subsequent reperfusion injury in the bladder.[78] In rats with overdistended bladder, maximal cystometric capacity and residual urine volume were increased, while voiding efficiencies were significantly decreased.

Pelvic Nerve Transection

Preganglionic axons emerge as the pelvic nerve from the sacral parasympathetic nucleus in the intermediolateral column of sacral spinal segments S2 to S4, and synapse in the pelvic ganglia, as well as in the small ganglia on the bladder wall, releasing acetylcholine. Bilateral pelvic nerve transection can create UAB, inducing urinary retention.[79]

Cryoinjury of Bladder

Our University of Pittsburgh laboratory has previously explored selective area UAB modeling using cryoinjury.[80,81] Under our experimental conditions, the cryoinjured bladder smooth muscle exhibited reproducibly impaired contractile parameters such that it may be applied as a model of insufficiently functioning smooth muscle.

Treatment

How Do We Currently Treat UAB?

Management of UAB is limited (Table 3); there are no validated, effective oral drugs available. Common treatment options include double void or straining to void and indwelling or intermittent catheterization. Standard pharmacotherapy includes the use of α-adrenergic blockers to reduce urethral outlet resistance and muscarinic agonists (eg, bethanechol) or choline esterase inhibitors (eg, distigmine).[1,82] However, analyses demonstrate few beneficial effects of these oral drugs, in addition to unfavorable effects. Harada and colleagues[83] reported that distigmine shows direct binding to muscarinic receptors in the rat bladder, and repeated

TABLE 3

Treatment Options for Underactive Bladder

Physiotherapy	**Current Status**
Double void, straining to void, indwelling, or intermittent catheterization	Conventional, recommended
Drug	
α-adrenoceptor antagonists	Available
Muscarinic receptor agonists (bethanechol, carbachol)	Available
Acethylcholinesterase (distigmine)	Available
Prostaglandin E_2	Potential
4 types of EP_2 receptors	Potential
Stem cell therapy	Promising
Gene therapy	
HSV-rhNGF	Promising

HSV-rhNGF, herpes simplex virus–encoding recombinant human nerve growth factor.

oral administration of distigmine causes downregulation of muscarinic receptors in the rat bladder, suggesting the therapeutic and/or side effects seen in the treatment of detrusor underactivity.

Potential UAB Treatment

Misoprostol, cholinesterase inhibitors, and cholinergic agents are potential candidates but there are concerns with their safety and lack of benefit.[1,82] Novel muscarinic receptor manipulation such as presynaptic M2 receptor antagonists or postsynaptic allosteric receptor enhancement could be promising.[84] Prokinetics used in gastroenterology and smooth muscle ionotropics used in cardiology may warrant consideration. It is established that PGE_2 can increase detrusor contraction and relax the urethra.[1,85] EP_1 and EP_3 receptors seem to mediate the excitatory bladder afferents of PGE_2 on afferent activity and smooth muscle, and EP_2 receptors are known to mediate bladder and urethra relaxation.[1] It would be interesting to test these receptor agonists in patients with UAB, and agents with this profile are currently under development.

Neuromodulation and intravesical electrical stimulation has been reported to be potentially beneficial in select patients. Use of stem cells and regenerative medicine may allow the weak detrusor to improve contractility and gene therapy to increase weak individual myocyte contractility with sarcoplasmic endoplasmic reticulum, calcium, magnesium, adenosine triphosphatase (SERCA).[86]

Sacral Nerve Stimulation

The guarding and voiding reflexes are activated at different times under completely different clinical scenarios. However, anatomically, they are located in close proximity in the S2–S4 levels of the human spinal cord.[87] Both sets of reflexes are modulated by a number of centers in the brain. Thus, these reflexes can be altered by a variety of neurologic diseases, some of which can unmask involuntary bladder activity mediated by C fibers.

It is possible to modulate these reflexes via sacral nerve stimulation (SNS) and restore voluntary micturition. Experimental animal data indicate that somatic afferent input to the sacral spinal cord can modulate the guarding and bladder-to-bladder reflexes. Sacral preganglionic outflow to the urinary bladder receives inhibitory input from various somatic and visceral afferents, as well as a recurrent inhibitory pathway.[88] Electrical stimulation of somatic afferents in the pudendal nerve elicits inhibitory mechanisms.[89] This is supported by the finding that interneurons in the sacral autonomic nucleus that exhibit firing correlated with bladder activity and were inhibited by activation of somatic afferent pathways. This electrical stimulation of somatic efferent nerves in the sacral spinal roots could inhibit reflex of detrusor overactivity mediated by spinal or supraspinal pathways.

In neonatal kittens and rats, micturition as well as defecation are elicited when their mother licks the perineal region.[89] This reflex appears to be the primary stimulus for micturition because urinary retention occurs when the young kittens and rat pups are separated from their mothers.

To induce micturition, the perineal afferents must activate the parasympathetic excitatory inputs to the bladder but must also suppress the urethral sympathetic and sphincter somatic guarding reflexes. A suppression of guarding reflexes by SNS contributes to enhancement of voiding in patients with urinary retention.

The perineal-to-bladder reflex is very prominent during the first 4 postnatal weeks and then becomes less effective and usually disappears in kittens by the age of 7 to 8 weeks, which is the approximate age of weaning. In adult animals and humans, perineal stimulation or mechanical stimulation of the sex organs inhibits the micturition reflex.[90-92]

Aside from the strong animal research that identified somatic afferent modulation of bladder and urethral reflexes, there are also data from clinical physiologic studies supporting the view that stimulation of sacral afferents can modify bladder and urethral sphincter reflexes. Functional electrical stimulation appears to be a favorable nonsurgical treatment for many patients with detrusor instability.

Stem Cell Therapy

Cell transplantation is not a new concept; however, the field of urologic tissue engineering has just recently grown to new and exciting levels. Because there is a general lack of regenerative ability in the bladder and urethral smooth muscle, research has centered on tissue repair by using pluripotent stem cells derived from other lineages. Our laboratory has focused on the isolation and characterization of a small population of these pluripotent stem cells that were derived from skeletal muscle.

Neuromodulation and intravesical electrical stimulation has been reported to be potentially beneficial in select patients. Use of stem cells and regenerative medicine may allow the weak detrusor to improve contractility and gene therapy to increase weak individual myocyte contractility with SERCA.

Using the pre-plate technique, we can purify and isolate cells that are highly capable of surviving post-transplantation and differentiating into other lineages.[93]

The rationale for using skeletal muscle for cellular-based gene therapy for the urinary tract is twofold. First, in contrast to smooth muscle, skeletal muscle is under constant repair of its damaged tissue due to the presence of satellite cells.[94] These cells are fusion-competent skeletal muscle precursors and, when differentiated, fuse to form myofibers capable of muscle contraction. Second, some purified satellite cells behave like pluripotent stem cells that may differentiate into another lineage.

The ability to harvest muscle-derived cells (MDCs), which contain satellite cells and stem cells from a skeletal muscle biopsy, has been previously demonstrated.[93,95-97] MDCs have been used for the delivery of secretory nonmuscle protein products such as human growth hormone and coagulation factor IX into the circulation.[98.99] In addition, when MDCs differentiate, they form myofibers that become post-mitotic and consequently exhibit long-term transgene persistence.[100]

We have also demonstrated that MDC transplantation increased muscle contractility in the cryoinjured detrusor model and nerve, or sphincter-injured, incontinence model.[101-105] Thus, transplantation of MDCs from skeletal muscle might be a promising treatment strategy for UAB.

Treatment of Diabetic Cystopathy

The first and most important step in the management of diabetes is to control blood glucose levels. Hyperglycemia has been proven to be related to neuropathy and other diabetes complications. However, the control of blood glucose levels does not mean the prevention of diabetic cystopathy.[9] Preventive management includes hypertension and hyperlipidemia control and an education for nonsmoking.

The main goals in diabetic cystopathy treatment are to avoid overdistension of the bladder and to decrease residual urine. Because diabetic cystopathy usually has an insidious onset, scheduled voiding should be recommended to all DM patients regardless of symptom presence. If needed, double or triple voiding may be also recommended.[106] Manual compression of lower abdomen (Credé maneuver) or abdominal straining (Valsalva maneuver) may be helpful to decrease residual urine in select patients. However, these maneuvers are contraindicated in the presence of increased intravesical pressure, vagal reflex, and vesicoureteral reflux. α-Blockers have some benefit in diabetic cystopathy concomitant with BOO. Cholinergic receptor agonists such as bethanechol chloride or urecholine have been used with inconsistent results in diabetic cystopathy.[107]

Loss of bladder sensation is irreversible in diabetes once it occurs and long-term follow-up is necessary. In addition, many patients with diabetic cystopathy may delay seeking urological evaluation because of insidious development of diabetic cystopathy that induces diminished sensation and increased bladder capacity. Thus, careful surveillance for voiding symptoms and screening for elevated residual urine, including urodynamic study, should be done regularly to prevent long-term complications secondary to diabetic cystopathy.

Future Treatment Strategies for Diabetic Cystopathy—Gene Therapy. Conservative treatments for diabetic cystopathy are limited and cannot restore bladder function, as mentioned previously. Following the efficacy of NGF treatment in basic studies,[108-110] the efficacy of NGF treatment in the clinical field has been reported.[111-113]

The feasibility of gene therapy using replication deficient herpes simplex virus (HSV) encoding recombinant human NGF (*rhNGF)* genes was reported. Four weeks after HSV-*rhNGF* injection into the STZ-DM rat bladder, significant increase of NGF levels in bladder and L6 dorsal root ganglia were detected. DM rats with HSV-NGF gene therapy also had smaller bladder capacity and residual urine than untreated DM rats.[114,115] Other reports using neurotrophic factors other than NGF, such as glial cell line–derived neurotrophic factor or NT-3, have also demonstrated significant efficacies in restoration of nerve functions in diabetic animals.[116,117]

Thus, in the future, neurotrophic factors or other growth factors combined with targeted gene therapy techniques may be beneficial for the therapy of patients with diabetic cystopathy.

Conclusions

UAB is an unmet medical need and a new frontier for study for the international academic and pharmaceutical/biotechnical industry community. Diabetic cystopathy is among the various diseases that may induce UAB, and is characterized by a loss of bladder sensation and detrusor underactivity. It is common and can develop insidiously. Tests, including urodynamic study in the early stages of diabetes, are needed. Exciting new approaches to treat diabetic cystopathy are currently being investigated. We believe UAB will be a fruitful area of research. ■

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MAIN POINTS

- Underactive bladder (UAB) is an unmet medical need that has received less attention than the condition of overactive bladder. Causes of UAB include neurogenic, myogenic, aging, and medication side effects. Symptoms include hesitancy, sensation of incomplete emptying, straining to void, and recurrent infections.
- UAB is usually observed with myogenic failures and when the following mechanisms are damaged: bladder peripheral afferent pathways, bladder peripheral efferent pathways, and lumbosacral spinal cord (spinal micturition center).
- Diabetic cystopathy has been described as impaired sensation of bladder fullness, increased bladder capacity, reduced bladder contractility, and increased residual urine. In addition to neuronal changes, recent studies suggest that diabetic cystopathy can result from an alteration in the physiology of the detrusor smooth muscle cell or urothelial dysfunction.
- The main goals in the treatment of diabetic cystopathy is to avoid overdistension of the bladder and to decrease residual urine. Because diabetic cystopathy usually has an insidious onset, scheduled voiding should be recommended to all diabetes patients regardless of symptom presence. If needed, double or triple voiding may be also recommended.
- Manual compression of lower abdomen or abdominal straining may be helpful to decrease residual urine in select patients; however, these maneuvers are contraindicated in the presence of increased intravesical pressure, vagal reflex, and vesico-ureteral reflux. α-Blockers have some benefit in diabetic cystopathy concomitant with bladder outlet obstruction. Cholinergic receptor agonists such as bethanechol chloride or urecholine have been used with inconsistent results in diabetic cystopathy.
- The changes of tissue neurotrophic factors such as nerve growth factors have been focused on as a convincing pathogenesis of diabetic neuropathy. The changes of neurotrophin-3 have also been reported. It is promising for future treatment strategies that the changes of tissue neurotrophic factor could play a critical role in inducing diabetic cystopathy.
- Treatments for diabetic cystopathy are limited and cannot restore bladder function. New treatment approaches for diabetic polyneuropathy, including diabetic cystopathy, have been reported in both the basic and clinical fields. In the future, neurotrophic factors or other growth factors combined with targeted gene therapy techniques may be beneficial for the management of patients with diabetic cystopathy.

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