Ultrastructural changes in the underactive bladder

Han-Chen Ho, Yang-Hsiang Hsu, Jia-Fong Jhang, Yuan-Hong Jiang, Hann-Chorng Kuo

INTRODUCTION

Detrusor underactivity (DU) and its symptom-based correlate underactive bladder (UAB) have gained renewed interest in the past few years [1]. DU is defined as a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span [2]. Patients with UAB/DU usually have a diminished bladder fullness or urgency sensation and cannot contract the detrusor sufficiently to complete bladder emptying. UAB is common in elderly patients, especially in patients with diabetes mellitus (DM), chronic illness, and central nervous system (CNS) disorders, but the actual prevalence is difficult to identify in a community-based study. It has been reported that 12%–48% of elderly patients with lower urinary tract symptoms might be caused by UAB [3]. It has been proposed that DU may result from dysfunction of any of the aspects responsible for the generation of a normal detrusor contraction, which can be myogenic or neurogenic [4]. The urodynamic study of UAB/DU may be characterized by a noncontractile detrusor, a low pressure, or poorly sustained detrusor contraction in association with a poor flow rate with or without a large post-void residual (PVR) volume [5]. Recent studies also revealed that the urothelial dysfunction of the urinary bladder may be associated with impaired bladder sensation as well as impaired detrusor contractility [6]. Patients with clinically UAB might have several contributing factors leading to difficult bladder emptying and large PVR.

ABSTRACT

Underactive bladder (UAB) is a symptom complex suggestive of detrusor underactivity (DU). Although it implies a primary dysfunction of the detrusor muscle, many other conditions such as advanced age, neurogenic factors, and bladder outlet obstruction also lead to UAB. The current understanding of the pathophysiology directly leading to UAB is limited. We believe that by identifying the morphological changes associated with UAB might shed light on this. Therefore, we searched literature with keywords of electron microscopy, ultrastructure, UAB, and DU to review current ultrastructural evidence concerning UAB.

KEYWORDS: Detrusor underactivity, Electron microscopy, Ultrastructure, Underactive bladder

CLINICAL CHARACTERISTICS OF UNDERACTIVE BLADDER

DU is common in patients with old age, general weakness, and with medical diseases such as DM, debilitating disease, cancer patients at terminal stage, or postmajor surgery [7]. A large proportion of patients with diabetic cystopathy have been found to have electrophysiologic evidence of neuropathy, and electrophysiologic evidence of neuropathy can moderately predict the presence of cystopathy [8]. In patients with UAB/DU, the intrinsic detrusor contraction speed is more compromised than intrinsic strength. When the intrinsic detrusor contraction speed (maximum detrusor contraction velocity) and intrinsic detrusor strength (isovolumetric detrusor pressure) are low, the patients were considered to have terminal phase of DU and had low voiding efficiency (<67% of bladder capacity) [9]. The duration of UAB/DU may be chronic or temporary. If the UAB/DU condition cannot be recovered after medical treatment or management, chronic UAB/DU is likely. In clinical practice, patients may regain voiding efficiency after recovery from illness, but some patients might develop chronic DU after acute illness. There must have some underlying pathogenesis for the development of transient UAB/DU, such as detrusor muscle damage or neurological inhibition which interfere the integration of musculomucosal mechanoreceptors, mucosal mechanoreceptors, and chemoreceptors [10].

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Pathophysiology of UAB

The causes of UAB/DU include DM, bladder outlet obstruction, aging, neurological diseases, spinal cord lesions, pelvic plexus, and infectious neurologic problems [11]. UAB/DU can result from the damage of the bladder afferent pathways, bladder efferent pathways, lumbosacral spinal cord, or pure detrusor failure [12]. The inhibitory effects of the bladder contraction by the striated urethral sphincter and the bladder neck (BN) via the alpha-adrenergic activity may also play a role for the development of UAB/DU. Patients with a severe cortical degenerative disease may lack of bladder perception and unable to initiate the voiding. Aging can cause structural and functional changes of the bladder afferent nerves and detrusor power, the reflex activity might also be impaired [13]. In addition, recent studies showed that urothelial dysfunction and altered sensory transduction pathways also play important roles in the pathophysiology of UAB/DU [14,15]. It is possible that the bladder urothelial dysfunction, sensory nerve dysfunction, detrusor myogenic dysfunction, as well as the impaired CNS control are involved in part, in the development of UAB/DU. In addition, bladder ischemia and repeated ischemia/reperfusion during a micturition cycle may also produce oxidative stress, leading to denervation and further tissue damage in the bladder wall [16].

There are still many unexplored pathophysiologies in the research needs for DU or UAB. Despite UAB/DU being a significant problem, historically it received a lack of attention and with little research invested in developing a better understanding of the problem and new treatments. Since morphology is closely related to function, we hereby review and delineate the ultrastructural changes of DU bladders, regarding the urothelium, detrusor muscles, and nerves. Hopefully, we could gain a better understanding of UAB/DU.

Urothelium

The urothelium lines the entire urinary tract and forms the interface between the urinary space and the underlying vasculature, connective, nervous, and muscular tissues [17]. Currently, numerous studies had proven that the urothelium not only acts as a barrier of the bladder, but also functions as an integral part of a sensory web which receives, amplifies, and transmits information about its external milieu [18]. Adenosine triphosphate (ATP) released from the urothelium has been suggested to have an essential role in the micturition reflex. It was shown that the mean level of ATP in the bladders of DU group was significantly lower than that in the control group [14]. In addition, several signaling molecules such as E-cadherin, muscarinic receptors (M2 and M3), P2 × 3 receptors, and endothelial nitric oxide synthase were reported to have significantly lower expression in patients with DU [15]. However, with the increasing interest of the potential role of urothelial and afferent dysfunction in DU, only few ultrastructural studies regarding urothelial integrity can be found. In the aging bladder, which is also a possible etiology of DU, an electron microscopic study revealed that the endolysosomes were generally much larger in umbrella cells than those observed in the younger rats, and the endolysosomes have a tendency to cluster in aged umbrella cells [19]. Another animal study found ultrastructurally swollen or completely destroyed mitochondria and accumulation of lipofuscin pigments in the aging bladder umbrella cells [20]. Nevertheless, similar morphological changes of endolysosomes or mitochondria in umbrella cells of human DU bladders have not been studied yet. Electron microscopy (EM) has been used to investigate the ultrastructure of bladders in patients with lower urinary tract diseases for the past 40 years [21-24]. In the interstitial cystitis/bladder pain syndrome (IC/BPS) bladders, EM study revealed large swollen epithelial cells with decreased amount of lateral processes [21]. Our previous study also applied EM to investigate the ultrastructure characteristics in the IC/BPS bladder and found the defects of the urothelial cell layers and integrity of umbrella cells [25]. In addition, these ultrastructure findings could be correlated to the clinical symptom severity. Although the lack of urothelial ultrastructural studies in DU limits further speculations, knowing that the morphological changes of the bladder may contribute to afferent activity, such studies might be helpful in identifying potential etiology and therapeutic targets.

Detrusor Muscle

Impaired detrusor activity has been considered as the major etiology of DU, causing prolonged bladder emptying and/or failure to achieve complete bladder emptying. Normal detrusor muscle lies deep to the lamina propria and consists of smooth muscle cells arranged into several compact fascicles [Figure 1]. Muscle fascicles were surrounded by perimysium, the interstitial connective tissue containing mostly collagen fibers with blood vessels and nerve terminals in between. Individual smooth muscle cells are separated by thinner interstitial septum. Under the EM, the intact sarcolemma and evenly distributed dense bodies are the characteristic of normal smooth muscle cells [Figure 2]. Detrusor dysfunction could

Figure 1: Normal detrusor muscle (DM) lies beneath the lamina propria (LP) and forming several muscle fascicles, separated by perimysium (arrow)
be attributed to aging, since aging in both sexes was associated with a decrease in the area density of smooth muscle to connective tissue ratio [26]. In addition to the increased detrusor fibrosis, the ultrastructural changes in the smooth muscle cells might also have impact on the pathogenesis of DU. Elbadawi et al. [22-24] investigated aging detrusor biopsies under EM and concluded three characteristic patterns: (1) dysjunction pattern between smooth muscle cells, (2) the dense band pattern in combination with widespread muscle cell and axon degeneration, and (3) hypertrophy of the smooth muscle cells. The widespread degeneration of muscle cells and axons superimposed on the dense band pattern was proposed as the structural correlate of impaired detrusor contractility after the authors evaluated the correlation between the ultrastructural changes with urodynamic studies [22]. Brierly et al. [27] conducted a controlled quantitative study of ultrastructural changes in the underactive detrusor. They reported that disruptive cell count in the DU bladder biopsies was significantly higher than the age-matched control specimens. Disruptive cells showed characteristics such as sarcoplasmic vacuolation, sequestration or blebbing, cell shriveling, cell fragmentation, and presence of cell debris in the intercellular spaces. Since there was no correlation between age and number of disruptive cells, the authors proposed that aging itself may not contribute to muscle disruption related with DU.

Between the bladder mucosa and detrusor, a group of myofibroblasts or interstitial cells are found which have a contractile phenotype and contain smooth muscle actin [28]. Currently, interstitial cells are believed to transmit the signals from the urothelium or detrusor. Impaired function of interstitial cells might cause diminished detrusor contractility through impaired bladder urothelial sensory input. The number of interstitial cells and the density of connexin 43 expressed on the cells are found to increase in overactive bladder [29]. However, the density of interstitial cells in the UAB/DU bladders has not been reported. In future, ultrastructural investigation of the interstitial cells might also reveal the possible deficits in patients with DU/UAB.

**NERVES**

Neurogenic factors are the other major etiology of UAB. Dysfunctions of the central neuronal control, peripheral motor, and sensory neuropathies may both contribute to DU by affecting the micturition reflex, detrusor contraction, and voiding. In normal human bladder, efferent nerve fibers of cholinergic neurons distributed in the detrusor muscle, and the released acetylcholine is the predominant neurotransmitter responsible for bladder contraction. The afferent innervation is mediated by myelinated A-delta fibers in the detrusor muscle and unmyelinated C-fibers located in the detrusor muscle, lamina propria [Figure 3], and adjacent to the urothelial cells [30]. However, studies on bladder neuronal ultrastructure are scarce. At the ultrastructural level, disrupted axonal structures with swollen perineurium and endoneurium were indicated to be involved in the progression to DU under the chronic ischemic rat model [31]. In human bladder biopsies with neurogenic dysfunction, degeneration of intrinsic detrusor nerves (such as reduced granular small vesicles, disrupted mitochondria, and collapsed axon) was suggested to potentially hinder efficient contraction of the detrusor muscle [32]. Nevertheless, more researches are needed to understand the complex interplay between the morphological changes and clinical symptoms.

**Figure 2:** Higher magnification of detrusor smooth muscle cells at (a) cross section and (b) longitudinal section. Smooth and intact sarcolemma of individual cell and evenly distributed dense bodies are shown. The endomysium (arrowhead) surrounding each individual cell is much thinner than the perimysium (arrow) surrounding muscle fascicles.

Afferent nerves of the pudendal nerve are postulated to have a potential modulatory effect on sympathetic neuronal control in various neuropathic and nonneuropathic bladder dysfunctions, but the mechanism and pathways remain unknown [33]. Patients with idiopathic DU may regain adequate detrusor contractility and resume spontaneous voiding [34,35] after transurethral incision of the BN (TUI-BN). Contractions of the urethral sphincter stimulate firing in muscle proprioceptive afferent nerves, which then activate the inhibition of bladder contraction and the micturition reflex [36]. TUI-BN might destroy the continuity of the BN and interrupt the inhibitory effect of bladder contractility. In an animal study, decreased urethral pressure by preganglionic pelvic nerve stimulation and administration of alpha, beta-methylene-ATP in female pigs also resulted in bladder detrusor contractions [37]. In addition, leakage of urine into the proximal urethra stimulated afferent nerves and induced or increased detrusor contractility [38]. These evidence might explain why patients with an UAB could regain bladder contractility after TUI-BN. Investigation of the parasympathetic and sympathetic nervous distributed in the bladder wall might also provide fruitful evidence for the pathophysiology of UAB/DU.

**Figure 3:** (a) Unmyelinated peripheral nerves (arrow) found in the lamina propria. (b) At higher magnification, lighter stained nerve terminals (*) are seen wrapped around the darker stained Schwann cell (S).
CONCLUSIONS

Patients with UAB/DU represent the difficulty in contracting the detrusor sufficiently to complete bladder emptying. This multifactorial condition has gained growing interest recently in the need of developing more accurate diagnostic criteria and better treatment plans. However, the research and published studies are still limited, especially in the field of bladder ultrastructure. A more thorough investigation of the morphological changes related to UAB/DU, especially the ultrastructures of urothelium, interstitial cells, and bladder afferent fibers, will facilitate our understanding of the pathophysiology of UAB/DU. In the long term, integration of clinical, functional, and morphological findings will provide the foundation for the development of more specific and effective pharmacotherapies of UAB/DU.

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Conflicts of interest

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REFERENCES

1. Chancellor MB, Bartolone SN, Lamb LE, Ward E, Zwaans BMM, Diokno A. Underactive bladder: review of progress and impact from the international CURE-UAB initiative. Int Neurourol J 2020;24:3-11.
2. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology in lower urinary tract function: Report from the standardisation sub-committee of the International Continence Society. Urology 2003;61:37-49.
3. Yu YD, Jeong SJ. Epidemiology of underactive bladder: Common but underresearched. Invest Urol 2017;58:S68-74.
4. Osman NI, Esperto F, Chapple CR. Detrusor underactivity and the underactive bladder: A systematic review of preclinical and clinical studies. Eur Urol 2018;74:633-43.
5. Thomas AW, Cannon A, Bartlett E, Ellis-Jones J, Abrams P. The natural history of lower urinary tract dysfunction in men: The influence of detrusor underactivity on the outcome after transurethral resection of the prostate with a minimum 10-year urodynamic follow-up. BJU Int 2004;93:745-50.
6. Birder LA, Ruggieri M, Takeda M, van Koeveringe G, Veltkamp S, Korstanje C, et al. How does the urothelium affect bladder function in health and disease? ICI-RS 2011. Neurourol Urodyn 2012;31:293-9.
7. Ueda T, Yoshimura N, Yoshida O. Diabetic cystopathy: Relationship to autonomic neuropathy detected by sympathetic skin response. J Urol 1997;157:580-4.
8. Bansal R, Agarwal MM, Modi M, Mandal AK, Singh SK. Urodynamic profile of diabetic patients with lower urinary tract symptoms: Association of diabetic cystopathy with autonomic and peripheral neuropathy. Urology 2011;77:699-705.
9. Cucchi A, Quaglini S, Rovereto B. Proposal for a urodynamic redefinition of detrusor underactivity. J Urol 2009;181:225-9.
10. Andersson KE. Detrusor underactivity/underactive bladder: New research initiatives needed. J Urol 2010;184:1829-30.
11. Miyazato M, Yoshimura N, Chancellor MB. The other bladder syndrome: Underactive bladder. Rev Urol 2013;15:11-22.
12. Chancellor MB, Blaivas JG. Classification of neurogenic bladder disease. In: Chancellor MB, editor. Practical Neuurology. Boston: Butterworth-Heinemann; 1995. p. 25-32.
13. Smith PP. Aging and the underactive detrusor: A failure of activity or activation? Neurourol Urodyn 2010;29:408-12.
14. Cho KJ, Koh JS, Choi J, Kim JC. Changes in adenosine triphosphate and nitric oxide in the urothelium of patients with benign prostatic hyperplasia and detrusor underactivity. J Urol 2017;198:1392-6.
15. Jiang YH, Kuo HC. Urothelial barrier deficits, suburothelial inflammation and altered sensory protein expression in detrusor underactivity. J Urol 2017;197:197-203.
16. Yamaguchi O, Nomiya M, Andersson KE. Functional consequences of chronic bladder ischemia. Neurourol Urodyn 2014;33:54-8.
17. Khandewal P, Abraham SN, Apodaca G. Cell biology and physiology of the uroepithelium. Am J Physiol Renal Physiol 2009;297:F1477-501.
18. Birder L, Andersson KE. Urothelial signaling. Physiol Rev 2013;93:653-80.
19. Truscheil SL, Clayton DR, Beckel JM, Yabes JG, Yao Y, Wolf-Johnston A, et al. Age-related endolysosome dysfunction in the rat urothelium. PLoS One 2018;13:e0198817.
20. Perše M, Injac R, Erman A. Oxidative status and lipofuscin accumulation in urothelial cells of bladder in aging mice. PLoS One 2013;8:e59638.
21. Collan Y, Alfhon O, Kivilaakso E, Oravisto KJ. Electron microscopic and histological findings on urinary bladder epithelium in interstitial cystitis. Eur Urol 1976;2:242-7.
22. Elbadawi A, Yalla SV, Resnick NM. Structural basis of geriatric voiding dysfunction. II. Aging detrusor: Normal versus impaired contractility. J Urol 1993;150:1657-67.
23. Elbadawi A, Yalla SV, Resnick NM. Structural basis of geriatric voiding dysfunction. III. Detrusor overactivity. J Urol 1993;150:1668-80.
24. Elbadawi A, Yalla SV, Resnick NM. Structural basis of geriatric voiding dysfunction. IV. Bladder outlet obstruction. J Urol 1993;150:1681-95.
25. Jiang JF, Ho HC, Jiang YH, Lee CL, Hsu YH, Kuo HC. Electron microscopic characteristics of interstitial cystitis/bladder pain syndrome and their association with clinical condition. PLoS One 2018;13:e0198816.
26. Lepor H, Sunaryadi I, Hartanto V, Shapiro E. Quantitative morphometry of the adult human bladder. J Urol 1992;148:414-7.
27. Brierly RD, Hindley RG, McLarty E, Harding DM, Thomas PJ. A prospective controlled quantitative study of ultrastructural changes in the underactive detrusor. J Urol 2003;169:1374-8.
28. Thompson SA, Copeland CR, Reich DH, Tung L. Mechanical coupling between myofibroblasts and cardiomycocytes slows electric conduction in fibrotic cell monolayers. Circulation 2011;123:2083-93.
29. Ikeda Y, Fry C, Hayashi F, Stolz D, Griffiths D, Kani A. Role of gap junctions in spontaneous activity of the rat bladder. Am J Physiol Renal Physiol 2007;293:F1018-25.
30. Ouslander JG. Management of overactive bladder. N Engl J Med 2004;350:786-99.
31. Zhao Z, Azad R, Yang JH, Siroky MB, Azadzoi KM. Progressives changes in detrusor function and micturition patterns with chronic bladder ischemia. Investig Clin Urol 2016;57:249-59.
32. Haferkamp A, Dörsam J, Resnick NM, Yalla SV, Elbadawi A. Structural basis of neurogenic bladder dysfunction. II. Aging detrusor: Normal versus impaired contractility. J Urol 2003;169:550-6.
33. Reitz A, Schmid DM, Curt A, Knapp PA, Schureb B. Afferent fibers of the pudendal nerve modulate sympathetic neurons controlling the bladder neck. Neurourol Urodyn 2003;22:597-601.
34. Peng CH, Kuo HC. Transurethral incision of bladder neck in treatment of
bladder neck obstruction in women. Urology 2005;65:275-8.
35. Jhang JF, Jiang YH, Kuo HC. Transurethral incision of the bladder neck improves voiding efficiency in female patients with detrusor underactivity. Int Urogynecol J 2014;25:671-6.
36. Thor KB, de Groat WC. Neural control of the female urethral and anal rhabdosphincters and pelvic floor muscles. Am J Physiol Regul Integr Comp Physiol 2010;299:416-38.
37. Dalmose AL, Rijkhoff NJ, Andersen IS, Stefania D, Jørgensen TM, Djurhuus JC. Bladder and urethral responses to pelvic nerve stimulation in the pig. Scand J Urol Nephrol Suppl 2002;210:34-45.
38. Jung SY, Fraser MO, Ozawa H, Yokoyama O, Yoshiyama M, De Groat WC, et al. Urethral afferent nerve activity affects the micturition reflex; implication for the relationship between stress incontinence and detrusor instability. J Urol 1999;162:204-12.