Association between Hyposensitivity of C-fiber Afferents at The Proximal Urethra and Storage/voiding Dysfunction in Female Patients with Detrusor Overactivity

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Purpose: We examined the associations between urethral sensation and storage/voiding function in female patients with detrusor overactivity (DO) by measuring urethral current perception threshold (CPT).

Materials and Methods: We retrospectively investigated the medical records of 27 consecutive patients with lower urinary tract symptoms who underwent cystometry, uroflowmetry (UFM), and urethral CPT tests from 2000 to 2015. Patients were classified into 2 groups: with/without DO. Seven DO-negative cases were selected as normal controls on cystometrogram (CMG) matching the inclusion criteria: bladder compliance $\geq$ 12.5 mL/cmH_2O, volume < 275 mL at first sensation, and no comorbidities possibly influencing micturition. Finally, 17 patients were included. Urethral CPT was evaluated with intraurethral square-wave impulses at 3 Hz to stimulate C-fibers. Urethral loss coefficient (LC), reflecting urethral resistance during voiding, was calculated by curve-fitting a mathematical model to a UFM waveform.

Results: Urge incontinence (UI) was observed in 7 DO-positive patients, but not in those with normal CMG. Urethral CPT and LC were significantly higher in patients with DO than in those with normal CMG. Median urethral CPT significantly increased in patients with both DO and UI than in those without these symptoms ($P < .005$). CPT values were correlated with the volume at first sensation (p=0.53, $P < .05$) and LC (p =0.59, $P < .05$). LC was not calculated in 3 cases due to poor curve-fitting.

Conclusion: In females, urethral C-fiber afferents may become hyposensitive as the detrusor becomes overactive with UI in the storage phase. During voiding, C-fiber hyposensitivity may relate to increased functional resistance of the urethra to urine outflow.

Keywords: current perception test; C-fiber; cystometry; detrusor overactivity; female; urethra; uroflowmetry

INTRODUCTION

Micturition depends on a complex neural control system to coordinate the activities of the lower urinary tract (LUT) consisting of the urinary bladder, urethra, and urethral sphincters.[1,2] During the storage phase, the guarding reflex (i.e., the bladder-to-urethral rhabdosphincter reflex) and the bladder-to-sympathetic reflex mainly contributes to urinary continence.[1-3] The storage phase can be switched to the voiding phase either involuntarily or voluntarily. The switching mechanism between the storage and voiding phases is mediated by the periaqueductal grey in the midbrain.[1-3] At the voiding phase, the pontine micturition center in the brainstem is released from the tonic inhibition of higher brain structures such as the hypothalamus and prefrontal cortex.[1-3] Subsequently, a long-loop spinobulbospinal voiding reflex that passes through the pontine micturition center is activated to initiate a contraction of the bladder and a relaxation of the urethral sphincter followed by an increase in bladder pressure and urinary outflow.[1-3] Thus, abnormalities in micturition suggests neural dysregulation of the reflex pathways between the urethra and bladder.[2,3] Increased frequency of voiding, urgency, urge urinary incontinence (UUI), and incomplete emptying of the bladder are clinically bothersome symptoms especially for the elderly people.[2,4]

The pelvic, hypogastric, and pudendal nerves transmit sensory information in afferent fibers from receptors in the LUT to second-order neurons in the lumbosacral spinal cord.[2,3] Afferent fibers traveling in the pelvic nerve to the sacral spinal cord are the most important for the initiation of micturition. Sacral afferent nerve terminals are uniformly distributed to all areas of the detrusor and urethra, whereas lumbar afferent nerve endings are most frequently found in the trigone and are scarce in the bladder body.[3] Two types of neural fibers constitute the afferent nerves: A-δ (myelinated) and C-fibers (unmyelinated).[2] The afferent axons in the urothelial submucosa and detrusor muscle are A-δ or C-fibers, while those in the mucosa are composed

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Table 1. Cystometric patterns and background diseases of the female patients

Case No.	Age (years)	Patterns of CMG	Pattern of DO	UUI	Background diseases / comorbidities
Pt_01	68	Normal CMG	Absence of DO	No	Diabetes mellitus
Pt_02	51	Normal CMG	Absence of DO	No	Endometriosis
Pt_03	63	Normal CMG	Absence of DO	No	Nervous pollakisuria
Pt_04	23	Normal CMG	Absence of DO	No	Nervous pollakisuria
Pt_05	69	Normal CMG	Absence of DO	No	Stress incontinence
Pt_06	45	Normal CMG	Absence of DO	No	Progressive muscular dystrophy
Pt_07	75	Normal CMG	Absence of DO	No	Osteoporosis
Pt_08	68	Idiopathic DO	Phasic DO	Yes	Nervous pollakisuria
Pt_09	84	Idiopathic DO	Phasic DO	No	Vertebral compression fracture (L1)
Pt_10	64	Neurogenic DO	Terminal DO	Yes	Cervical cancer (radical hysterectomy, postoperative)
Pt_11	54	Neurogenic DO	Terminal DO	No	Cervical cancer (radical hysterectomy, postoperative)
Pt_12	78	Neurogenic DO	Phasic DO	Yes	Rectal cancer (trans-anal resection, adjuvant radiation therapy)
Pt_13	70	Neurogenic DO	Terminal DO	Yes	Cerebral infarction (left hemiplegia)
Pt_14	51	Neurogenic DO	Terminal DO	Yes	Multiple sclerosis, subacute myelo-optico-neuropathy
Pt_15	14	Neurogenic DO	Phasic DO	No	Spina bifida (postoperative)
Pt_16	75	Neurogenic DO	Terminal DO	Yes	Diabetes mellitus, bladder diverticulum
Pt_17	76	Neurogenic DO	Terminal DO	Yes	Spinal canal stenosis (lumber)

of C-fiber alone.[2,5] Physiologically, A-δ afferents fire at low thresholds by responding to passive bladder distention and active detrusor contraction.[2] C-fibers are primarily activated by a low temperature, chemicals, inflammation or noxious stimulation under pathological conditions.[2] Since the firing threshold is higher in C-fibers than A-δ afferents, the C fiber activation is not physiologically involved with normal micturition.[2] Measurement of current perception threshold (CPT) is semi-objective evaluation of LUT sensation.[6-8]. Kenton et al.[8] reported that the urethral CPT is significantly higher in older females symptomatic of UUI, indicating that urethral sensation may be potentially impaired in parallel with aging and appearance of overactive bladder (OAB) symptoms. We previously demonstrated significant differences in the CPT of C-fiber afferents at the proximal urethra among 53 patients with neurogenic DO, idiopathic DO, or normal configuration and specifically between the patients with and without UUI on filling cystometry, suggesting that urethral C-fiber hyposensitivity may underlie the appearance of UUI.[9] However, it remains unclear how such an impairment of the urethral C-fiber afferents affects urination. There are more complex relations between the bladder and the proximal urethra in men than in women. In the present study, we investigated the relationships between cystometric/uroflowmetric parameters and urethral CPT values in female patients for simple interpretation.

PATIENTS and METHODS

Study patients

We retrospectively identified consecutive eighty patients with lower urinary tract symptoms (LUTS) who underwent urodynamic study and urethral CPT determination in Yamagata University Hospital from 2000 to 2015. The exclusion criteria were male gender (n=46) and missing data on uroflowmetry (n=7). The remaining 27 females were divided into DO-positive or -neg-

Table 2. Clinical background of seventeen female patients

	DO-positive, n=10 (%)		Normal CMG, n=7 (%)		*P; U*-test
Patterns of DO; phasic / terminal DO	4 (40.0%) / 6 (60.0%)		0 (0.0%) / 0 (0.0%)		
Qualification according to cause of DO;					
Idiopathic / neurogenic DO	2 (20.0%) / 8 (80.0%)		0 (0.0%) / 0 (0.0%)		
Urge urinary incontinence	7 (70.0%)		0 (0.0%)		
	Median	Range	Median	Range	
Age (years)	69	14 −84	63	23 −75	0.241
Filling cystometry and CPT test					
First sensation of bladder filling (mL)	136.0	37.0 −343.0	85.0	34.0 −158.0	0.187
Maximum cystometric capacity (mL)	254.1	34.9 −476.5	403.0	197.5 −625.0	0.055
Compliance (mL/cmH2O)	12.7	1.9 −145.7	116.8	40.0 −357.5	< 0.005
Urethral CPT(mA)	9.7	3.6 −26.0	3.0	1.0 −5.2	< 0.005
Free uroflowmetry					
Qmax (mL/s)	8.4	3.7 −16.9	16.5	5.2 −37.2	0.172
VV (mL)	100.3	20.5 −343.3	171.6	49.0 −442.0	0.133
PVR (mL)	28.6	0 −117.0	12.4	0 −85.0	0.404
Loss coefficienta	3.42	1.06 −15.36	2.01	0.20 −2.26	< 0.01
LCi	0.17	0.12 −0.50	0.07	0.05 −0.30	0.124
LCf	1.11	0.00 −9.43	0.49	0.01 −0.59	0.240
LCe	2.83	0.92 −9.64	1.38	0.03 −1.50	< 0.01

Abbreviations: CMG, cystometrogram; DO, detrusor overactivity; CPT, current perception threshold; Qmax, maximum flow rate; VV, voided volume; PVR, post void residual.

a Loss coefficients cannot be calculated in patients with DO-positive (n=1) and normal CMG (n=2) due to insufficient curve fitting. LCi, LCf, and LCe indicate loss coefficients due to inertial, frictional and elastic resistances in the urethra, respectively.

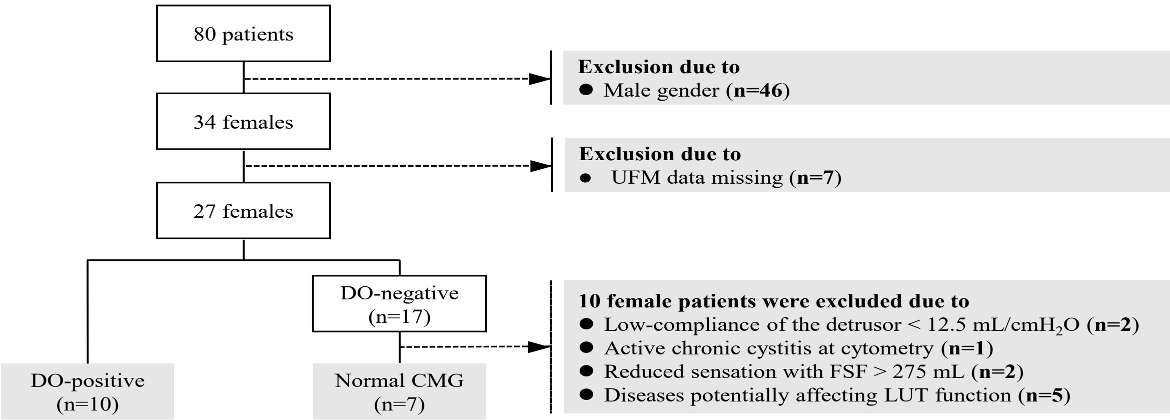

Figure 1. Flow chart of female patients' classification
Abbreviations: DO: detrusor overactivity; CMG: cystometrogram; UFM: uroflowmetry; FSF: first sensation of bladder filling; LUT: lower urinary tract

ative groups according to cystometric observations (n=10 and n=17, respectively). Seven of the 17 patients without DO who met the criteria of compliance ≥ 12.5 mL/cmH2O[10], bladder volume at the first sensation of bladder filling (FSF) < 275 mL, and no diseases potentially causing LUT dysfunction were designated as normal controls on cystometrogram (CMG). Finally, 17 female patients were eligible for the analyses (**Fig. 1**). None of the patients in the study had detrusor-sphincter dyssynergia (DSD) on CMG with electromyogram or urethral stricture at insertion of a 14Fr electric stimulating catheter for urethral CPT measurement.

The present study was approved by the ethical committee of the Yamagata University Faculty of Medicine (No. 217, approved on September 5, 2018). The requirement for individual informed consent was waived, because the present study was retrospective and the anonymity of the participants was ensured. This study has conformed with the ethical standards in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Urodynamic study

Water-filling cystometry with electromyography, uroflowmetry and ultrasonographic measurement of postvoid residual (PVR) were performed in conventional procedures as described elsewhere.[9]

CPT measurement of the proximal urethra

Detailed procedures for CPT measurement were previously depicted.[9,11] Briefly, immediately after filling cystometry, CPT was determined at the proximal urethral mucosa by evaluating C-fiber sensation as stim-

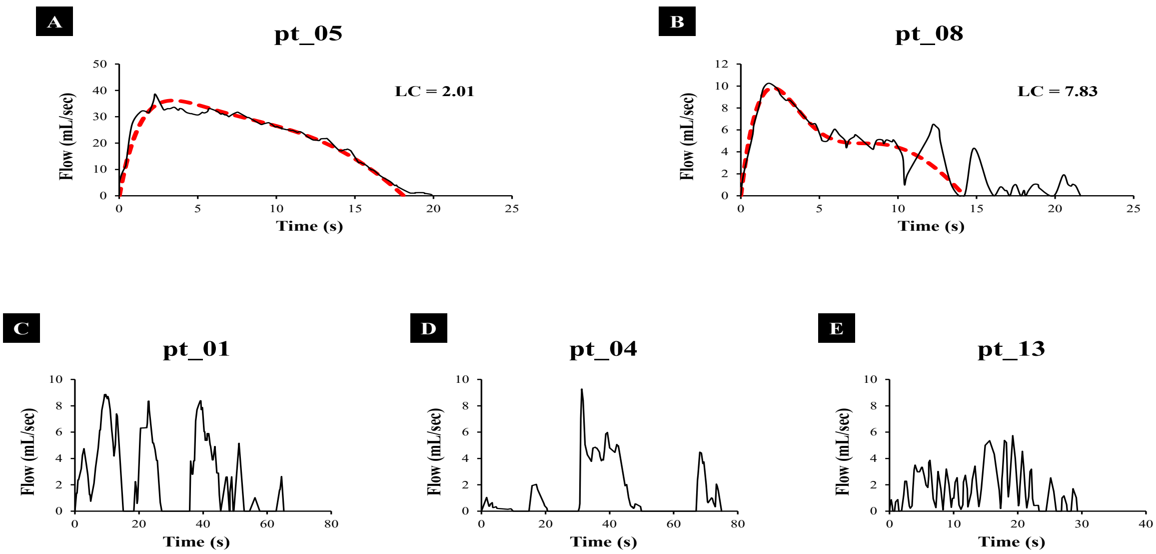

Figure 2. Approximation of actual UFM curves with a mathematical model
Actual traces of UFM were sufficiently curve-fitted to the mathematical model.(13-15) Representative cases of normal CMG (pt_05) and positive DO (pt_08) are shown in **Fig. 2A** and 2B, respectively. However, the model was not applicable in 3 cases (pt_01, 04, and 13) because of abnormal UFM waveforms (**Fig. 2C, D, and E**, respectively). Continuous and dashed lines in the panels indicate actual traces of UFM and approximation with the mathematical model, respectively. Here, patient numbers in the parenthesis are compatible with those presented in Table 1.
Abbreviations: DO: detrusor overactivity; CMG: cystometrogram; UFM: uroflowmetry; LC: loss coefficient

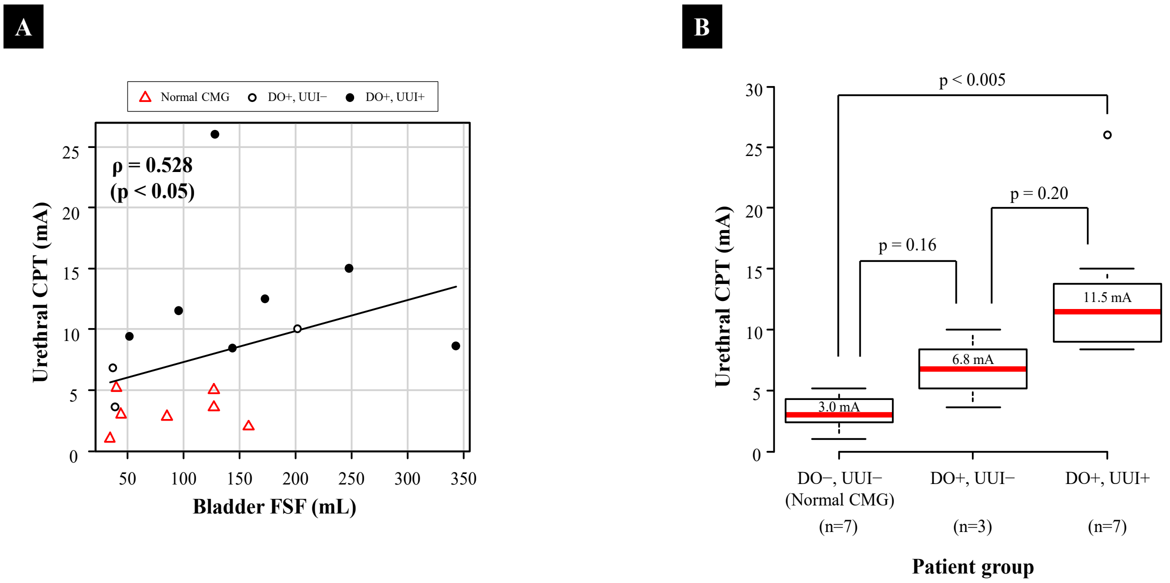

Figure 3. CPT values at the proximal urethra. **(A)** Association between urethral CPT and bladder FSF. Positive correlation between median CPTs at the proximal urethra and FSF on filling cystometry for patients with and without DO was demonstrated on the scatter plot. **(B)** Differences in urethral CPT among patient groups with normal CMG, DO, and/or UUI. Median CPTs were 11.5, 6.8, and 3.0 mA for the 3 groups of DO+ and UUI+, DO+ and UUI−, and normal CMG, respectively, with statistical significance between patients with both DO and UUI and those with neither. Note that patients with normal CMG exhibited neither DO nor UUI.
Abbreviations: CPT: current perception threshold; DO: detrusor overactivity; CMG: cystometrogram; UUI: urge urinary incontinence; +: positive; −: negative; FSF: first sensation of bladder filling;

ulation impulses (0.5-ms square-wave, 3 Hz) applied via transurethral electrodes were gradually increased to patients' first perception of the impulses.[7,12] The least intensity of the electrical stimulation at first perception was defined as urethral C-fiber CPT at the proximal portion.[7,12]

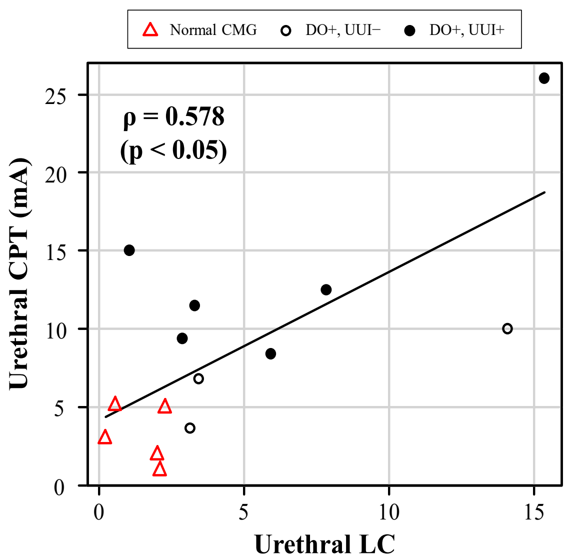

Figure 4. Association between urethral CPT and LC. Urethral CPT was positively correlated with urethral LC. Note that patients with normal CMG were all plotted near the origin. Three patients were omitted from this graph due to the unavailability of LC calculation. Abbreviations: CPT: current perception threshold; DO: detrusor overactivity; CMG: cystometrogram; UUI: urge urinary incontinence; LC: loss coefficient

Calculation of urethral loss coefficient during the voiding phase

Urethral loss coefficient (LC) can be calculated from the relation of kinetic energy and pressure loss obtained by approximating UFM waveforms using a mathematical voiding model.[13-15] In brief, urine-expelling is dynamically considered as a balanced consequence of intravesical pressure as a driving force and an outlet resistance system of the urethra. The resistance system consists of inertial, frictional and elastic resistances. The interaction among these dynamic factors changes in a time course (during voiding) and is expressed as a UFM curve. The pressure differences against the inertial, frictional, and elastic resistances are proportional to the change in urinary flow rate in a time course (dQ(t)/dt), urinary flow rate (Q(t)), and the voided volume (VV) at the moment (∫Qdt), respectively. Herein, the intraurethral pressure difference (ΔP(t)) can be described as follows:

$$\Delta P(t) = L\frac{dQ}{dt} + RQ + \frac{1}{C}\int Q\,dt \qquad (1)$$

where L, R, and C are constants that can be determined by the curve-fitting of actual UFM configurations with the mathematical model (Figure 2A and B).[13,15] The integral values of pressure loss during voiding time contributing to urethral inertial, frictional, and elastic resistances (Δ_{Pi}, Δ_{Pf}, and ΔP_e, respectively), and the energy used for inertial resistance is Wi. In the present study, we defined urethral LC as follows:

$$Urethral\ LC = \frac{\Delta P_i + \Delta P_f + \Delta P_e}{W_i} = LC_i + LC_f + LC_e \qquad (2)$$

where LC_i, LC_f, and LC_e indicate loss coefficients due to inertial, frictional, and elastic resistances in the urethra, respectively.

Statistical analysis

Statistical analysis was done non-parametrically using the Mann-Whitney *U* test, Kruskal-Wallis test, and post-hoc test with the Steel-Dwass method between groups. Spearman's correlation analysis was performed to examine the relationships between the 2 groups. Statistical significance was considered with *p*-value < 0.05. All statistical analyses were done using R3.4.1 (http://cran.r-project.org/, accessed on June 30, 2017).

RESULTS

Table 1 shows the background diseases of the 17 patients. The study patients were classified into 2 groups according to the CMG findings: normal CMG (n=7) and DO-positive (n=10). **Table 2** shows the clinical data on the types of DO, UUI, age, sex, and urodynamic study results in the 2 groups of patients. Patients' age, the volume at FSF, and maximum cystometric capacity did not vary between the groups. However, the median values of bladder compliance and urethral CPT were significantly different between the groups (Mann-Whitney *U*-test, $P < .05$). As for the UFM parameters, peak flow rate (Qmax), VV, and PVR appeared to have better median values in patients with normal CMG, but the differences between the 2 groups did not reach statistical significance.

Figure 3A demonstrates that the urethral CPT values were significantly correlated with bladder capacity at FSF on filling cystometry (Spearman's correlation coefficient, p =0.528, $P < .05$). Figure 3B shows significant differences in the median CPT values of the urethra among patients with normal CMG, DO, and/or UUI (Kruskal-Wallis test, $P < .005$). Median urethral CPT significantly increased in patients with both DO and UUI compared to those with neither (post-hoc test with the Steel-Dwass method, $P < .005$; **Figure 3B**). Patients who exhibited urodynamic DO without symptomatic UUI had urethral CPT values that were intermediate between those of the 2 groups of patients. LC could not be calculated in 3 cases (n=1 and n=2 for groups with DO and normal CMG, respectively) due to poor curve-fitting of the mathematical model to the individual actual traces of UFM configurations (**Figure 2C, D, and E**). Urethral LC was significantly larger in DO-positive patients than in those with normal CMG (*U*-test, $P < .01$; **Table 2**). LC_e, one of the 3 components constituting a total value of urethral LC, contributed mainly to the difference in urethral LC between the 2 groups (*U*-test, $P < .01$; **Table 2**). Figure 4 shows a positive correlation between the urethral CPT values and LC for the entire cohort in the present study (Spearman's correlation coefficient, p =0.578, $P < .05$).

DISCUSSION

Urgency and UUI are not necessarily observed clinically in patients who exhibit DO in CMG tests.[16] However, easy excitability of bladder C-fiber afferents has been regarded as the underlying mechanism for urgency and DO.[2,5] The number of urgency and UUI episodes was found to have a significantly negative correlation with bladder CPT values determined at 5-Hz stimuli to C-fiber activation.[17] The proximal urethral C-fibers were significantly hyposensitive to electrical stimulation (1-5 Hz) in patients with OAB, UUI, and/or other pathological conditions.[8,18-20] Kenton et al.[11] described that impaired sensation of the urethra in UUI female patients restored after a 2-month administration of tolterodine for detrusor relaxation. OAB patients showed significantly more DO, more hypersensitivity, and lower CPT of the bladder compared with non-OAB patients.[17]

In the present study, the proximal urethra became more hyposensitive to C-fiber stimuli, in parallel with the increased volume at FSF and the emergence of DO and/or UUI. These findings support the conclusion that the C-fiber impairment of the urethra may work synergistically with DO to cause UUI in female patients. However, the development of DO in female patients with early-stage type II diabetes was not associated with the dysfunction of intravesical C-fibers.[21] In the present study, we were unable to refer to this point because bladder CPT determination was out of the investigation. However, positive correlation between urethral CPT values and bladder volumes at FSF in our study may indicate that bladder A-δ afferents became impaired together with urethral C-fiber hyposensitivity in the female patients.

Various reflexes between the urethra and bladder that are activated to facilitate or inhibit urination by sensory signals from the proximal urethra have been identified.[2,6,22] The urethral afferents fire in response to fluid flow in the urethra, with an increasing tendency of the firing rate in proportion to increases in the flow.[23] Sensory input from the urethra has been found to initiate bladder contractions in the quiescent bladder and augment ongoing contractions in ewes[24], rats[25,26], and humans.[27,28] Administered into the urethral lumen, prostaglandin E2 activates the micturition reflex via stimulation of C-fiber afferent nerves.[22] Similarly, capsaicin increases the bladder contraction frequency within a few minutes after intraurethral administration.[22,26] By contrast, silencing urethral afferents with anesthesia reduces bladder contraction frequency and bladder emptying efficiency.[25-27] In patients with benign prostatic hyperplasia (BPH), prostatic urethral anesthesia resulted in significant increases in first sensation volume and maximum cystometric capacity.[22] Bladder neck and urethral injections of botulinum toxin significantly lessened LUTS and increased Qmax in mild BPH patients, accompanied by a transient increase in bladder capacity and decrease in PVR at 1 and 3 months after treatment.[29] Thus, sensory information from the proximal urethra modulates the afferent activities to influence micturition.[22] Accordingly, a positive correlation between urethral CPT and LC values in the present study support that sensory impairment of the proximal urethral C-fibers may be involved in functional rigidity of the urethra during voiding.

UFM with PVR measurement is a widely used first-line urodynamic test in urologic practice for screening patients with suspected LUT dysfunction.[30] The test provides objective and quantitative information on voiding, and the patterns of the UFM curve may reflect certain types of voiding abnormality.[30] In general, a multichannel pressure/flow (PF) study is required for a detailed investigation because the shape of the UFM curve is largely affected by detrusor contractility, bladder outlet resistance, and/or bladder volume.[30] However, the PF study is cumbersome, invasive, and costly compared with UFM. In the PF study, examinees are asked to store and void urine under the non-physiological condition of 2 catheters that are indwelled via the urethra and anal canal to record intra -vesical and -abdominal pressures, respectively. In addition, electrodes are attached to the perineal/perianal regions to electromyographically monitor sphincter activities.

From the perspective of energy balance, we have put proposed a novel analytical theorem of UFM curves based on the premise that energy produced by intravesical pressure as a driving force during voiding should be equivalent to the sum of the energy consumed by the resistance systems through the urethra and the kinetic energy of urine outflow from the urethral outlet.[13-15] In the present study, the resistance systems were defined as comprising the inertial, frictional, and elastic resistances of the urethra. Using this theorem, urethral LC, a type of urethral resistance, can be calculated from the kinetic energy and pressure loss obtained by the mathematical approximation of UFM waveforms.[13,14] and PF relationships during voiding can be plotted.[13-15] We reported that urethral LC in BPH patients who undertook transurethral resection of the prostate significantly decreased after the surgery, to the levels comparable with normal women and men with unobstructed bladder outlet.[14]

In the present study, urethral LC and the elastic component of the LC (LC_e) were significantly higher in DO-positive patients than in those with normal CMG. These findings suggest a possible association between urethral rigidity during voiding and hyposensitivity of C-fiber afferents in the proximal urethra, considering that neither anatomical stenosis of the urethra nor DSD were found in the study cohort. There were no statistical differences in Qmax, VV, and PVR between the DO-positive and normal CMG groups in the present study, which may be attributable to the small number of patients, all-female cohort, and/or lack of healthy subjects referenced as a control. Herein, the patients with normal CMG had higher values of urethral LC than did normal females in a previous study[14], which may be because patients with normal CMG potentially suffer from C-fiber impairments of the proximal urethra owing to unknown etiologies, given the general vulnerability of the C-fiber afferents[2,22]. In this retrospective study, we were unable to examine the relationships among CPT, urethral LC, and PF parameters, including detrusor contractility and obstruction grade, since no patients undertook urodynamic evaluation with a conventional PF study for LUTS.

The present study includes some limitations in data interpretation.[1] The study was retrospectively designed based on only a small number of female patients.[2] Reference controls for comparison of CPT were set to patients with normal CMG, but not healthy volunteers.[3] CPT test for LUT has not been a methodologically standardized procedure.[5,12] In this situation, the bladder CPTs of A-δ and C -fibers were not determined.[4,21] Data on subjective evaluation of LUTS severity were lacking. [5] We did not perform a conventional PF study for evaluating voiding dysfunction, and calculation of urethral LC from UFM curves is not yet common in the urology field. Thus, large-scale and prospectively designed studies are further required to confirm and validate the present results.

CONCLUSIONS

Urethral C-fiber hyposensitivity was significantly related to urodynamic DO and/or UUI during urine storage as well as increased urethral LC at voiding in LUTS females. The firing threshold of urethral C-fiber afferents may increase to weaken the continence mechanism according as the detrusor becomes overactive. When the storage phase of the bladder is switched to the voiding phase, the C-fiber impairment of the proximal urethra may associate with the increase in functional rigidity of the urethra during urine outflow.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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