Original Article - Lower Urinary Tract Dysfunction

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Changes in transient receptor potential vanilloid 1 and transient receptor potential vanilloid 4 in patients with lower urinary tract dysfunction

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Purpose: We investigated the association between transient receptor potential vanilloid (TRPV) expression in human urothelium tissue and lower urinary tract dysfunction (LUTD).

Materials and Methods: We prospectively enrolled men who planned to undergo surgical treatment for benign prostatic obstruction to analyze TRPV1 and TRPV4 expression in the urothelium using enzyme-linked immunosorbent assay and immunofluorescence staining. Patients were divided into two groups based on urodynamics: the detrusor underactivity (DU) group and the non-DU group. Levels of TRPV1 and TRPV4 were compared between the two groups. We also divided patients into two groups according to degree of subjective urinary urgency symptoms using a 5-point urinary sensation scale and compared the differences in TRPV1 and TRPV4 levels between the two groups. The correlations between urodynamic parameters with TRPV1 or TRPV 4 in all patients were also analyzed.

Results: The levels of TRPV1 and TRPV 4 were not significantly different between the DU group (n=10) and the non-DU group (n=11). When we divided the patients according to degree of subjective urgency, the level of TRPV1 was not significantly different between the urgency group (n=10) and the non-urgency group (n =11), but the level of TRPV4 was significantly increased in the urgency group (p=0.029). There was no significant correlation between the level of TRPV1 or TRPV4 and urodynamic parameters in any patients.

Conclusions: TRPV4 could be a useful diagnostic biomarker for patients with LUTD.

Keywords: Detrusor underactivity; Lower urinary tract symptoms; Overactive bladder; Transient receptor potential channel

INTRODUCTION

Lower urinary tract dysfunction (LUTD) can be difficult to diagnose solely on the basis of symptoms or noninvasive testing approaches, and an invasive diagnostic tool for urodynamic study (UDS) is sometimes required. Thus, the role of video UDS, which requires radiation exposure, has increased [1]. However, there are several limitations to UDS, and it can be difficult to determine its suitability based on patient symptoms because some aspects of the pathophysiology of LUTD are under debate. Many studies have investigated the pathophysiology of LUTD, and the role of the uro-

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thelium is attracting attention. The urothelium is involved in bladder function and releases various neurotransmitters in response to external stimuli, such as mechanical, chemical, and thermal neurotransmitters [2]. The urothelium can affect not only sensory aspects but also detrusor contraction. Research has suggested that the urothelium is involved in the pathogenesis of detrusor underactivity (DU) and overactive bladder (OAB) [3].

Transient receptor potential vanilloid (TRPV), which is permeable to Ca^{2+} and regulates various Ca^{2+}-dependent cellular events, is one of the ionic channels expressed within the urothelium [4]. Several human and animal studies have shown that urothelial TRPV1 expression is increased in OAB and is related to LUTD [5-7]. TRPV4 in the urothelium and detrusor muscle could be involved in a mechanosensory pathway and may represent detrusor overactivity (DO) or DU in LUTD [8]. However, to date, most studies have been performed in animals, and evidence is lacking in humans. Therefore, more human studies are needed to be able to use TRPV1 or TRPV4 to diagnose LUTD and to establish consistency with current diagnostic tools such as UDS or symptom questionnaires for LUTD. We therefore investigated changes in TRPV1 and TRPV4 in the urothelium using UDS and symptoms in patients with LUTD associated with benign prostatic obstruction to determine whether TRPV could be used as a diagnostic biomarker for LUTD.

MATERIALS AND METHODS

1. Study population and design

Men aged 50 to 75 years who were planning to undergo surgical treatment for benign prostatic obstruction, such as transurethral resection of the prostate or Holmium laser enucleation of the prostate, were prospectively enrolled from April 2019 to May 2020. All enrolled patients underwent UDS, which was conducted in accordance with the International Continence Society good urodynamic practice recommendations [9], and all patients agreed to provide bladder tissue samples. Patients who had any one of the following were excluded from this study: (1) diagnosis of prostate cancer before or after surgery for benign prostatic obstruction, (2) history of prostatic or urethral surgery, (3) history of acute urinary tract infection within 1 month, (4) interstitial cystitis/bladder pain syndrome, (5) bladder cancer, (6) bladder stone, and (7) indwelling bladder catheterization for more than 1 month. This study was performed in accordance with the guidelines of the Declaration of Helsinki. All participants provided written informed consent prior to enrollment. This study was reviewed and approved by the Institutional Review Board of our hospital (approval number: HIRB-20190125-038).

To obtain bladder specimens, three cold-cup biopsies of healthy mucosa of the bladder posterior wall were performed after the bladder was filled with 150 to 200 mL normal saline just before the onset of prostate surgery. The specimens were dissected under a microscope to separate the tissue from the detrusor muscle and were frozen in liquid nitrogen until the experiment was conducted. Expression of TRPV1 and TRPV4 in the urothelium was evaluated with enzyme-linked immunosorbent assay (ELISA) and immunofluorescence staining. Patients were divided into two groups: the DU group of subjects with a bladder contractility index less than 100 in urodynamics and the non-DU group with a bladder contractility index equal to or greater than 100. The levels of TRPV1 and TRPV4 were compared between the two groups. In addition, we divided patients into two groups according to the degree of subjective urinary urgency using a 5-point urinary sensation scale [10] and compared the differences in levels of TRPV1 and TRPV4 between the two groups. The urgency group was defined as patients with combined urgency ≥4 on the 5-point scale. The correlations between urodynamic parameters with TRPV1 or TRPV 4 in all patients were also analyzed.

2. ELISA and immunofluorescence staining for TRPV

For ELISA, the tissue was rinsed with and homogenized in 1× phosphate-buffered saline (PBS). After two freeze-thaw cycles were performed, the homogenate was centrifuged at 2℃ to 8℃ for 5 minutes at 5,000×*g*. The levels of TRPV1 and TRPV4 in the specimen were measured according to the manufacturer's instructions using a human TRPV1 ELISA kit and a human TRPV4 ELISA kit (Cusabio Biotech Co., Houston, TX, USA). The optical density of each well was measured within 5 minutes with a microplate reader (VersaMax; Molecular Devices Co., San Jose, CA, USA) set to 450 nm. For immunofluorescence staining, bladder tissues were fixed in 4% paraformaldehyde and rinsed with PBS. The slides were exposed to blocking solution at room temperature for 2 hours to inhibit nonspecific signal. The tissue sections were incubated with antibodies to TRPV1 (1:500; Abcam Ltd., Cambridge, UK) and TRPV4 (1:600; Novus Biologicals, Centennial, CO, USA) at 4℃ overnight. After washing three times with PBS, the slides were incubated with secondary antibody, Alexa Fluor 488-labeled goat anti-rabbit IgG (1:600; Molecular Probes, Eugene, OR, USA), at room temperature for 2 hours. Slides were stained with 4',6-diamidino-2-phenylindole (Vector Laboratories, Burlingame, CA, USA), and

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Table 1. Clinical characteristics and urodynamic findings of enrolled patients

Variable	Total (n=21)	DU group (n=10)	Non-DU group (n=11)	p-value	Urgency group (n=10)	Non-urgency group (n=11)	p-value
Age, y	66.9±0.8	67.7±1.3	66.1±0.9	0.349	65.6±0.9	68.0±1.1	0.132
BMI, kg/m^2	25.7±0.6	26.1±0.8	25.4±0.8	0.557	26.0±0.8	25.5±0.7	0.605
PSA, ng/mL	3.1±0.6	2.9±0.5	3.3±1.1	0.654	4.1±1.1	2.1±0.5	0.132
Total prostate volume, mL	61.5±5.5	61.5±8.4	61.5±7.6	0.863	68.6±8.7	55.1±6.5	0.223
Transitional zone volume, mL	29.8±2.6	31.1±4.5	28.5±2.8	0.912	32.1±3.1	27.9±4.0	0.295
IPSS total	17.9±1.7	18.7±2.3	17.1±2.8	0.546	22.0±2.7	14.6±1.7	0.055
IPSS storage subscore	7.3±0.8	7.1±0.9	7.4±1.2	1.000	9.4±1.1	5.6±0.6	0.021*
IPSS voiding subscore	10.6±1.2	11.5±1.7	9.7±1.6	0.436	12.6±1.6	9.0±1.5	0.122
IPSS QoL score	3.6±0.2	3.5±0.2	3.6±0.4	0.666	3.7±0.2	3.4±0.3	0.633
Urodynamic parameters							
Qmax, mL/s	7.1±0.8	4.7±0.6	9.2±1.1	0.001*	7.3±1.2	6.8±1.0	0.756
Voided volume, mL	188.9±25.6	119.8±26.4	251.7±33.3	0.005*	218.2±37.3	162.2±34.9	0.282
PVR, mL	194.1±38.9	232.1±44.8	159.6±62.5	0.173	105.2±35.6	275.0±58.2	0.061
MCC, mL	394.4±26.1	370.3±31.9	416.4±40.8	0.468	332.8±34.5	450.5±31.1	0.016*
PdetQmax, cmH_2O	67.1±6.8	43.2±6.1	88.9±6.9	<0.001*	85.6±8.7	50.3±7.4	0.006*
BOOI	52.9±6.4	33.8±6.2	70.4±7.7	0.002*	70.8±8.1	36.7±6.6	0.006*
BCI	102.4±9.1	66.7±6.8	134.8±7.7	<0.001*	122.4±12.5	84.2±10.9	0.036*

Values are presented as mean±standard error of the mean.
DU, detrusor underactivity; BMI, body mass index; PSA, prostate-specific antigen; IPSS, International Prostate Symptom Score; QoL, quality of life; Qmax, maximal flow rate; PVR, postvoid residual; MCC, maximum cystometric capacity; PdetQmax, detrusor pressure on maximal flow; BOOI, bladder outlet obstruction index; BCI, bladder contractility index.
*Statistically significant.

a BX 50 microscope (Olympus, Tokyo, Japan) was used for fluorescence visualization.

3. Statistical analysis

All data are reported as means with standard error of the mean. We compared clinical characteristics including urodynamic parameters and TRPV between patients with and without DU and between patients with and without urgency. The comparison was performed using the Mann–Whitney U-test for all continuous variables. We analyzed the correlations between TRPV and urodynamic parameters using Spearman correlation analysis. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). A p-value <0.05 indicated a significant difference.

RESULTS

The clinical characteristics and urodynamic findings of the enrolled patients are shown in Table 1. When urodynamic parameters were compared by degree of subjective urgency, the urgency group (n=10) had lower maximum cystometric capacity, higher bladder outlet obstruction index, and higher bladder contractility index than the non-urgency group (n=11). The levels of TRPV1 and TRPV4 were not significantly different between the DU group (n=10) and the non-DU group (n=11). When we divided the patients according to degree of subjective urgency, the level of TRPV1 was not significantly different between the urgency and non-urgency groups, but the level of TRPV4 was significantly increased in the urgency group (2.025±0.324 vs. 0.607±0.005, p=0.029) (Fig. 1). There were no significant correlations between the level of TRPV1 or TRPV4 and urodynamic parameters in any patients (Table 2).

Immunofluorescence staining revealed that TRPV1 and TRPV4 were localized in the urothelium. As shown by the immunofluorescence signals on image analysis, there were no significant differences between the DU and non-DU groups. However, the image analysis indicated differences in the immunofluorescence signals of TRPV4 between the urgency and non-urgency groups (Fig. 2).

DISCUSSION

In this study, we did not identify any significant differences in TRPV1 or TRPV4 expression in the urothelium according to DU and based on UDS. We were also not able to confirm significance when we analyzed the correlations between TRPV and urodynamic parameters. However, we found a significant difference in TRPV4 expression between

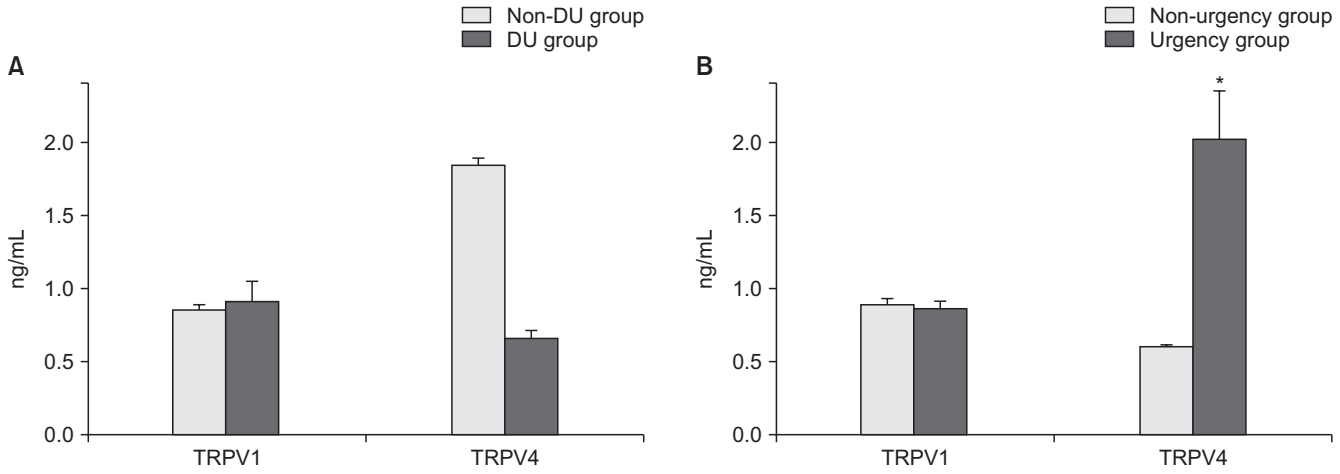

Fig. 1. Comparisons of TRPV1 and TRPV4 expression levels (A) between the DU group and non-DU group and (B) between the urgency group and non-urgency group. TRPV, transient receptor potential vanilloid; DU, detrusor underactivity. *Significant difference between the two groups ($p<0.05$).

Table 2. Correlation of TRPV1 and TRPV4 with urodynamic parameters

Parameter	TRPV1		TRPV4	
	r	p-value	r	p-value
Qmax	-0.172	0.456	-0.095	0.684
VV	-0.343	0.128	0.029	0.902
PVR	0.277	0.225	-0.308	0.175
MCC	-0.012	0.96	-0.433	0.05
PdetQmax	-0.134	0.563	0.33	0.144
BCI	-0.118	0.61	0.233	0.31
BOOI	-0.119	0.606	0.373	0.096

TRPV, transient receptor potential vanilloid; Qmax, maximal flow rate; VV, voided volume; PVR, postvoid residual; MCC, maximum cystometric capacity; PdetQmax, detrusor pressure on maximal flow; BCI, bladder contractility index; BOOI, bladder outlet obstruction index.

the two groups according to urgency.

There are several hypotheses for how TRPV can affect the function of the lower urinary tract. The main hypothesis is that TRPV1 and TRPV4 are related to stretch-evoked ATP release from the urothelium. Absence of TRPV1 or TRPV4 via a genetic deletion of the channel in mice results in low threshold afferent responses with decreased bladder contraction and enhanced bladder storage function, such as increased bladder capacity and increased bladder compliance [11,12]. TRPV1 knockout mice have reduced ATP levels and depressed bladder afferent responses to purinergic stimulation compared with wild-type mice [13]. Blockage of TRPV4 by intravesical administration of TRPV4 antagonist in mice leads to chronic urothelial overexpression of nerve growth factor and a significant decrease in distension-evoked urothelial ATP release [14]. Because reduced release of ATP in DU has been demonstrated in animal and human studies [15,16], a change in expression of TRPV1 or TRPV4 in DU can be expected. Actually, a significant upregulation of TRPV4 expression in the urothelium is noted in female rats with bilateral pelvic nerve crush, a DU animal model [17]. Vesical administration of TRPV4 agonist improves bladder dysfunction in DU, but the improvement is not seen in TRPV4 knockout rats because there is no TRPV4 as a treatment target for DU [18]. However, our study did not demonstrate significant changes in TRPV1 or TRPV4 expression in the DU group. The differences between our study and previous studies are that our study was conducted in men, and not in animals or women, and that we enrolled patients with DU caused by bladder outlet obstruction, which was defined by a UDS index called the bladder contractility index, and not DU caused by pelvic nerve injury. In addition, the DU group in our study included some patients with severe urgency (3/10, 30%), who may have experienced DO and impaired contractility. Ultimately, there might be limitations for defining DU if patient symptoms are not considered and DU is classified only by UDS. Additionally, there are several downsides to UDS that should be considered before interpretation [19]. Also, there are no standard, detailed urodynamic definitions or diagnostic criteria for DU related to complex bladder pathophysiology [20]. This issue was a limitation of our study and a limitation of UDS in the diagnosis of LUTD. Correlations between UDS parameters and TRPV were not demonstrated in our study, and one of the reasons for this might be the small sample size.

When we analyzed the change in TRPV expression according to patient symptoms, TRPV4 expression was significantly associated with urgency, whereas TRPV1 expression was not. Our previous animal research showed an increase

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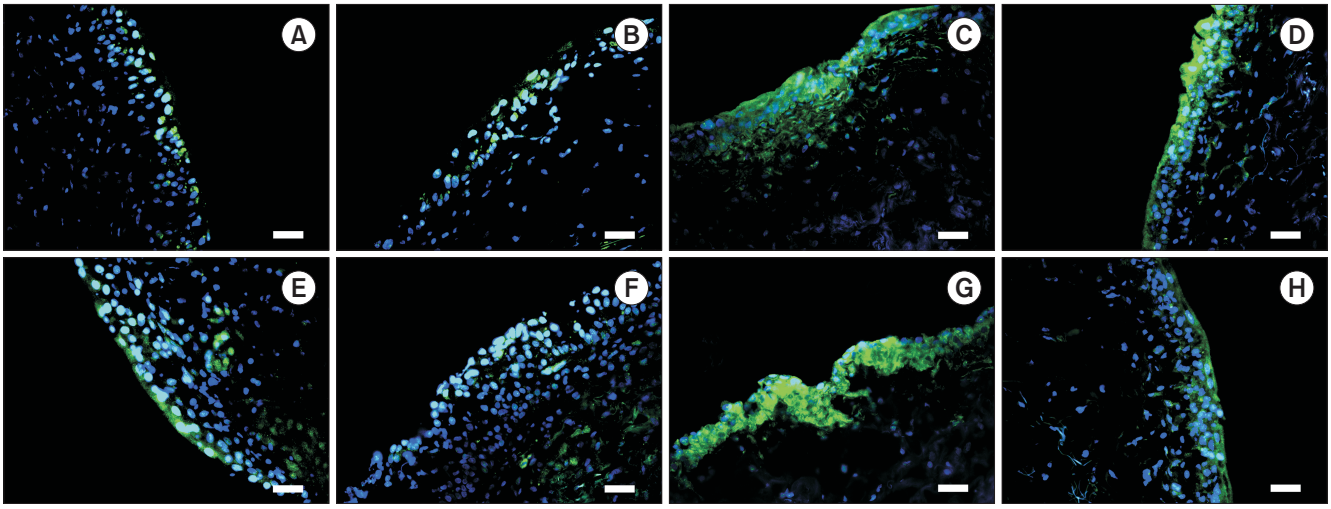

Fig. 2. Immunofluorescence staining of TRPV1 and TRPV4. (A) TRPV1 in the DU group. (B) TRPV1 in the non-DU group. (C) TRPV4 in the DU group. (D) TRPV4 in the non-DU group. (E) TRPV1 in the urgency group. (F) TRPV1 in the non-urgency group. (G) TRPV4 in the urgency group. (H) TRPV4 in the non-urgency group. Scale bars: 200 μm. TRPV, transient receptor potential vanilloid; DU, detrusor underactivity.

in TRPV4 expression in the urothelium from DO-associated bladder outlet obstruction and the beneficial effect of TRPV antagonists on DO [21]. Roberts et al. [22] demonstrated TRPV4 upregulation in aging and OAB by experiments using urothelium from guinea pig and patients with idiopathic OAB. The suggested mechanisms of action for these reported results are ATP release from the urothelium, intracellular Ca^{2+} change, and superoxide release. The hypotheses are supported by the results of various experiments using both TRPV4 agonists and antagonists.

Some previous studies have suggested that TRPV1 may be involved in DO. Shimura et al. [23] reported that upregulated TRPV1 in urothelial cells of patients with lower urinary tract symptoms is positively correlated with urgency urinary incontinence and reflects the severity of OAB. Reduction of bladder TRPV1 expression by early intravesical administration of TRPV1 desensitizing agonist after spinal cord injury has been shown to improve bladder function in neurogenic rats with DO, with a decrease in intravesical pressure and amplitude of bladder contractions [24]. Although other studies have shown that TRPV1 expression is higher in patients with idiopathic OAB than in healthy controls [5,25], we did not find a relationship between TRPV1 and urgency in this study. Most previous studies were conducted in women, but our study was conducted in men. Although the exact reason is not known, this sex difference might have impacted the expression of TRPV1 in OAB. In one animal study, TRPV1 expression in the bladder was significantly lower in men than in women [26].

There were some additional limitations to this research. Due to technical limitations, TRPV1 and TRPV4 expression were investigated on the basis of samples from bladder tissue that contained some nonurothelial tissues. However, that would not have had a significant impact on our results because TRPV4 is mainly expressed in the urothelium, and the expression of TRPV4 in nonurothelial tissue is low [18,27]. Moreover, for ethical reasons, it was difficult to obtain bladder tissue samples through invasive procedures in healthy control patients, so we were not able to include a healthy control group without bladder outlet obstruction. If healthy control patients could have been added to the comparisons of the change in TRPV expression according to LUTD subtype, a more specific trend in TRPV expression by LUTD may have been established. However, this type of analysis will require development of methods to accurately identify changes in TRPV in the human lower urinary tract less invasively. Another limitation of this study is that the case number was small. Although we conducted a power analysis on sample size, we would have reached more reliable conclusions if we had used more patients. In addition, TRPV levels could be affected by clinical factors such as the duration of LUTD symptoms or the use of medications. Nevertheless, it was not easy to design an analysis of the impact on TRPV of these factors; this limitation should be considered when interpreting the results of this study.

Because of technical limitations, the methods used in our study are time consuming and invasive. Thus, the results of this study are challenging to apply in actual clinical practice right away. However, if the technology for TRPV evaluation is further advanced in the future or if the relationship between TRPV4 expression in the urine and urothelium is defined by further study, we could apply our study findings

to clinical practice with benefits to cost and patient ethics in the evaluation of LUTD.

CONCLUSIONS

In this study, we did not identify a significant difference in TRPV1 or TRPV4 expression when LUTD was classified on the basis of UDS, but we did identify a significant difference in TRPV4 expression when LUTD was classified on the basis of symptoms of urgency. Because TRPV expression based on LUTD classification from symptoms cannot be investigated in an animal model, additional approaches in human research subjects can be helpful. To accurately diagnose LUTD, both UDS and patient symptoms should be considered; however, there is still uncertainty about the approach to diagnosis. Therefore, new biomarkers such as TRPV are needed, and our results provide valuable evidence that TRPV4 in the urothelium may play a role.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Joon Chul Kim. Data acquisition: Kang Jun Cho and Jun Sung Koh. Statistical analysis: Jin Bong Choi. Data analysis and interpretation: Kang Jun Cho. Drafting of the manuscript: Kang Jun Cho. Critical revision of the manuscript: Kang Jun Cho and Joon Chul Kim. Obtaining funding: Kang Jun Cho. Administrative, technical, or material support: Sang Hi Park and Weon Sun Lee. Supervision: Joon Chul Kim. Approval of the final manuscript: Joon Chul Kim.

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