

## ERECTILE DYSFUNCTION

# Which Happens Earlier, Lower Urinary Tract Symptoms or Erectile Dysfunction?



Yohei Matsuda, MD, PhD, Ko Kobayashi, MD, PhD, Fumimasa Fukuta, MD, PhD, Akio Takayanagi, MD, PhD, Kohei Hashimoto, MD, PhD, Toshiaki Tanaka, MD, PhD, and Naoya Masumori, MD, PhD

## ABSTRACT

**Introduction:** Although an association between erectile dysfunction (ED) and lower urinary tract symptoms (LUTS) has been suggested, it was not clarified whether LUTS developed before ED or vice versa.

**Aim:** To clarify whether LUTS develop before ED or vice versa and which symptoms predicted the onset of the other condition in a longitudinal community-based study.

**Methods:** We conducted a longitudinal community-based study on LUTS and ED in aged Japanese men. A follow-up study was conducted to determine their longitudinal changes of LUTS and ED after 15 years. Erectile function was evaluated using a validated questionnaire. LUTS were evaluated based on the International Prostate Symptom Score, quality of life index, and prostate volume.

**Main outcome measure:** We evaluated the baseline symptoms among the participants who had LUTS and ED in the follow-up survey and what prior symptoms could predict the onset of the other condition using the data from a long-term longitudinal survey.

**Results:** A total of 108 men were enrolled in this study. Of the 47 men having both LUTS and ED in the follow-up study, men having only LUTS ( $n = 16$ ) were more frequent than those having only ED ( $n = 6$ ) in the initial study. Likewise, of the 38 men having both nocturia and ED at the time of the follow-up study, those having only nocturia ( $n = 12$ ) were more frequent than those having only ED ( $n = 5$ ) in the initial study. In multivariable analysis, age 60 years or older (odds ratio: 7.10, 95% CI: 2.09-24.13) and nocturia (odds ratio: 15.83, 95% CI: 3.05-82.15) were independent predictors for the onset of ED.

**Conclusion:** There were more men with prior onset of LUTS, especially nocturia, than men with prior onset of ED among those with both ED and LUTS in this long-term longitudinal study. Nocturia may be a predictor of subsequent ED. **Matsuda Y, Kobayashi K, Fukuta F, et al. Which Happens Earlier, Lower Urinary Tract Symptoms or Erectile Dysfunction?. J Sex Med 2021;9:100275.**

Copyright © 2020, The Authors. Published by Elsevier Inc. on behalf of the International Society for Sexual Medicine. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**Key Words:** Benign Prostatic Hyperplasia; Nocturia; Sexual Dysfunction; Longitudinal Study; Community-Based Study

## INTRODUCTION

Recently, an association between erectile dysfunction (ED) and lower urinary tract symptoms (LUTS) has been suggested in some clinical studies.<sup>1-3</sup> The Multinational Survey of the Aging Male was a large-scale, multinational survey to investigate the relationship between LUTS and sexual dysfunction in older

men<sup>1</sup>. This study revealed that the presence and severity of LUTS were risk factors for sexual disorders in aging males.<sup>1</sup> Similarly, some studies demonstrated the relationship between the variables of LUTS (voiding symptoms, nocturia and quality of life [QOL] score) and erectile function.<sup>2,3</sup>

When there are 2 associated pathophysiological conditions, one disease occurs before the other. For example, for ED and cardiovascular disease, men aged 40-49 years with a new diagnosis of ED had a nearly 50-fold increase in the incidence of coronary artery disease over 10 years.<sup>4</sup> Therefore, ED warrants further screening for cardiovascular disease.

With regard to LUTS and ED, it was not clarified whether LUTS developed before ED or vice versa. To clarify the relationship, we need data from a long-term survey. Therefore, the

Received March 9, 2020. Accepted October 13, 2020.

Department of Urology, Sapporo Medical University School of Medicine, Sapporo, Japan

Copyright © 2020, The Authors. Published by Elsevier Inc. on behalf of the International Society for Sexual Medicine. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.esxm.2020.10.003>

**Table 1.** Participant characteristics

Variables	Initial study		Follow-up study		P value
	Median	Interquartile range	Median	Interquartile range	
Age (years)	57	49-65	71	64-80	<0.01
Total IPSS	7	4-10	9	4-11	0.01
IPSS 1 (not empty)	1	0-2	1	0-1	0.81
IPSS 2 (day frequency)	1	0-2	1	1-2	0.67
IPSS 3 (stop/start)	0	0-1	1	0-1	0.70
IPSS 4 (urgency)	1	0-1	1	0-2	0.07
IPSS 5 (weak stream)	1	0-2	1	1-2	0.01
IPSS 6 (straining)	1	0-2	1	0-1	0.50
IPSS 7 (nocturia)	1	0-2	1	1-3	<0.01
QOL score	2	1-3	2	1-4	0.02
PV (mL)	17.7	15.4-21.6	24.3	17.9-32.6	<0.01
Erectile rigidity score	5	3-5	2	1-4	<0.01

ED = erectile dysfunction; IPSS = International Prostate Symptom Score; PV = prostate volume; QOL = quality of life.

purpose of this study was to clarify which condition developed before the other and which symptoms predicted the onset of the other condition using the data of a 15-year longitudinal community-based cohort study in Japan.

## MATERIALS AND METHODS

### Study Design and Inclusion Criteria

We conducted a longitudinal community-based study to determine the prevalence of benign prostatic hyperplasia and LUTS and to investigate the sexual function of men in Shimamaki-mura, Hokkaido, Japan, in 1992<sup>5</sup> and 2007.<sup>6</sup> In 1992, 319 of the 682 (47%) men aged 40-79 years who resided in Shimamaki-mura participated in the baseline study. In 2007, 185 men survived and still resided in Shimamaki-mura. Of the remaining 134, 96 had died and 38 had moved away.<sup>6</sup> 135 of the 185 (73%) survivors participated in the follow-up study. 27 participants were excluded from this analysis because of medical histories that affected urinary and sexual function. The exclusion criteria were lumbar surgery (n = 10), bladder cancer (n = 3), prostate cancer (n = 7), medical treatment for cerebral vascular disease (n = 7), neurogenic bladder (n = 1), administration of an antiandrogen (n = 2), initiation of hemodialysis (n = 1), and incomplete data (n = 8). 15 of the excluded participants had received alpha-blocker medication.

### Evaluation of Erectile Function and LUTS

Erectile function was evaluated using a self-administered validated Japanese questionnaire.<sup>7,8</sup> Participants were queried about the rigidity of their erection (1 = flaccid to 6 = fully rigid). In the present study, ED was defined as 3 (the penis is hard but not hard enough for penetration) or less.

LUTS were evaluated based on the International Prostate Symptom Score (IPSS),<sup>9</sup> QOL index, and prostate volume (PV).

The PV was measured by a single examiner in each survey and estimated using a previously reported formula.<sup>6,10-12</sup>

### Statistical Analysis

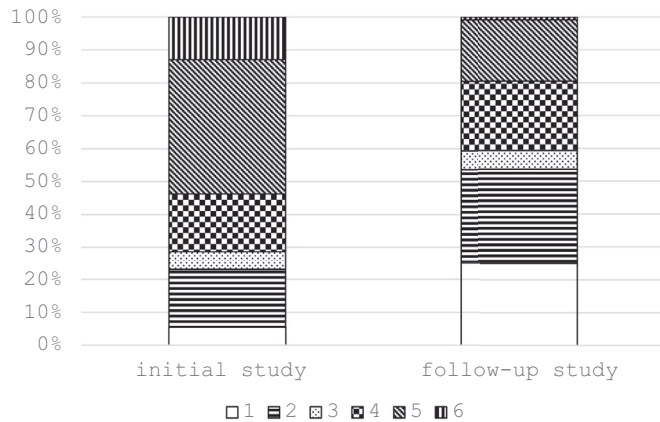
We first evaluated the baseline symptoms among the participants who had LUTS and ED in the follow-up survey. Second, we evaluated what prior symptoms could predict the onset of the other condition using the data from a long-term longitudinal survey. The cutoff points of these variables were age  $\geq 60$  years, total IPSS  $\geq 8$ ,<sup>13</sup> individual IPSS  $\geq 2$ , QOL index  $\geq 2$ , and PV  $\geq 20$  mL in this statistical analysis. We defined these cutoff points for baseline variables in reference to previous reports and the presence of symptoms. The cutoff point of age was according to the World Health Organization definition of an older person.<sup>14</sup> The cutoff point of the PV used the average PV in Japanese.<sup>10</sup> The difference of each symptom over time was analyzed using the Wilcoxon signed-rank test. Using the chi-square test and logistic regression analysis, we evaluated whether these variables could predict the onset of ED or LUTS. We used several factors for the variables of multivariable analysis with reference to a previous study that reported the association between LUTS and ED. A *P*-value of <0.05 was regarded as statistically significant. All statistical analyses were performed using StatView 5.0 for Windows (SAS Institute, Cary, NC).

This study was approved by the Review Board of Sapporo Medical University Hospital (February 2007, No. 18-9).

## RESULTS

### Characteristics in the Initial and Follow-Up Studies

A total of 108 men were enrolled in this study. The median follow-up period was 14.4 years (range: 13.8-15.3 years). At the time of the baseline study, their median age was 57 years. The median total IPSS, QOL score, and PV were 7, 2, and 17.7 mL, respectively. The total IPSS, QOL score, and PV showed a



**Figure 1.** Results of the evaluation of erectile function in each study. Rigidity of erection—1: flaccid, 2: slightly hard, 3: hard but not hard enough for penetration, 4: hard enough for penetration but not completely hard, 5 almost completely hard, 6: fully rigid. Erectile dysfunction was defined as 3 (penis is hard but not hard enough for penetration) or less. The rigidity score in the follow-up study was significantly decreased compared with the score in the baseline study ( $P < .01$ ).

significant increase with age (Table 1). Nocturia (IPSS Q7) also increased significantly. The median rigidity score in the baseline study was 5 and that in the follow-up study was 2 (Table 1). The numbers of subjects with each rigidity score in the baseline study were 6 (5.6%), 19 (17.6%), 6 (5.6%), 19 (17.6%), 44 (40.8%), and 14 (13.0%) for scores 1 to 6, respectively. In the follow-up study, these numbers changed to 27 (25.0%), 31 (28.7%), 6 (5.6%), 23 (21.3%), 20 (18.5%), and 1 (0.9%) for scores 1 to 6, respectively (Figure 1). Thus, the rigidity score showed a significant decrease with age ( $P < .01$ ). There were 77 (71.3%) men without ED in the baseline study, and 64 (59.3%) men had ED at the time of the follow-up study. In the baseline study, men without LUTS and ED were most prevalent. However, men with LUTS and ED became most prevalent in the follow-up study (Table 2). Similarly, men without nocturia and ED were most prevalent in the baseline study, and men with nocturia and ED became most prevalent in the follow-up study.

**Table 2.** Distribution of having lower urinary tract symptoms and ED or not

Symptoms	Baseline study (1992)	Follow-up study (2007)
LUTS (-)/ED (-)	n = 46 (42.6%)	n = 21 (19.4%)
LUTS (+)/ED (-)	n = 31 (28.7%)	n = 23 (21.3%)
LUTS (-)/ED (+)	n = 13 (12.0%)	n = 17 (15.7%)
LUTS (+)/ED (+)	n = 18 (16.7%)	n = 47 (43.5%)
Nocturia (-)/ED (-)	n = 62 (57.4%)	n = 30 (27.8%)
Nocturia (+)/ED (-)	n = 15 (13.9%)	n = 14 (13.0%)
Nocturia (-)/ED (+)	n = 14 (13.0%)	n = 26 (24.1%)
Nocturia (+)/ED (+)	n = 17 (15.7%)	n = 38 (35.2%)

ED = erectile dysfunction; LUTS = lower urinary tract symptoms.

**Table 3.** Distribution of previous symptoms which men with LUTS and ED had

Current symptoms	Previous symptoms
LUTS (+)/ED (+) n = 47	LUTS (-)/ED (-) n = 9 (19.1%)
	LUTS (+)/ED (-) n = 16 (34.0%)
	LUTS (-)/ED (+) n = 6 (12.8%)
	LUTS (+)/ED (+) n = 16 (34.0%)
Nocturia (+)/ED (+) n = 38	Nocturia (-)/ED (-) n = 6 (15.8%)
	Nocturia (+)/ED (-) n = 12 (31.6%)
	Nocturia (-)/ED (+) n = 5 (13.2%)
	Nocturia (+)/ED (+) n = 15 (39.5%)

ED = erectile dysfunction; IPSS = International Prostate Symptom Score; LUTS = lower urinary tract symptoms.

LUTS was defined as a total IPSS score of 8 or more.

Nocturia was defined as nighttime frequency of 2 times or more.

ED was defined as an erectile rigidity score of 3 (the penis is hard but not hard enough for penetration) or less.

### Relations Between Erectile Function and LUTS

At the time of the follow-up study, 47 men had developed LUTS and ED simultaneously. In the baseline study, whereas the onset of LUTS preceded ED in 16 men, the onset of ED preceded LUTS in 6 men. Moreover, similar results were obtained for nocturia and ED. 38 men had nocturia and ED in the follow-up study. In 12 of them, nocturia developed previously. On the other hand, the onset of ED preceded nocturia in 5 men (Table 3).

In addition, we evaluated the relationship between the onset of ED and variables of LUTS at baseline to clarify what variables of LUTS could predict the onset of ED. Table 4 shows the results of univariate and multivariable analyses using the chi-square test and logistic regression test to clarify the predictors for ED. According to previous studies that demonstrated the relationship between the variables of LUTS and erectile function,<sup>2,3</sup> we used the total IPSS score, nocturia (IPSS Q7), and QOL score as variables of LUTS in multivariable analysis for evaluating predictors of ED. In this analysis, age 60 years or older (odds ratio: 7.10, 95% CI: 2.09-24.13) and nocturia (IPSS Q7  $\geq 2$ ) (odds ratio: 15.83, 95% CI: 3.05-82.15) were independent predictors for the onset of ED.

### DISCUSSION

ED and LUTS are common problems for the aging male. Several large-scale cross-sectional community-based studies<sup>1,15-20</sup> and surveys of patients with benign prostatic hyperplasia/LUTS<sup>21,22</sup> revealed the relations between sexual dysfunction and LUTS. On the other hand, there are few reports using the data from longitudinal analysis. Furthermore, there has been little focus on the variables of LUTS or ED that could

**Table 4.** Results of univariate and multivariable analyses using the chi-square test and logistic regression test to clarify the predictors for ED

Variables	Cutoff	Univariate analysis		Multivariable analysis	
		<i>P</i> -value	OR	95% CI	<i>P</i> -value
Age (years)	≥60	<.01	7.10	2.09–24.13	<.01
Total IPSS	≥8	.05	1.50	0.46–4.97	.51
Nocturia (IPSS Q7)	≥2	<.01	15.83	3.05–82.15	<.01
QOL index	≥2	<.05	0.48	0.14–1.64	.24
PV (mL)	≥20	.05	2.69	0.25–28.92	.41

ED = erectile dysfunction; IPSS = International Prostate Symptom Score; OR = odds ratio; PV = prostate volume; QOL = quality of life.

predict the onset of the other. Thus, the predictors remain unknown.

Using the baseline data of the Medical Therapy of Prostatic Symptoms study, it was suggested that severe LUTS (American Urological Association Symptom Index score 20 or greater),<sup>23</sup> age, less education, and obesity were significantly associated with poor sexual function (sexual drive, erectile function, sexual problem assessment, and overall sexual satisfaction). On the other hand, in the longitudinal cohort of that study, none of these baseline variables predicted the decline of sexual function during follow-up. However, the average observation period of that study was only 4.5 years. Therefore, the results for the longitudinal cohort might be insufficient to indicate that the variables of LUTS or ED cannot anticipate the onset of the other for the aging male.

Many animal studies have evaluated the relationship between LUTS and ED. One of these studies reported the onset of ED after LUTS/bladder outlet obstruction.<sup>24</sup> In the study, the erectile function of rats with bladder outlet obstruction was impaired after 16 weeks of obstruction. This animal model suggested that ED could be induced by LUTS/bladder outlet obstruction. In the present study, we suggest that LUTS, especially nighttime frequency, may predict the onset of ED. It is very interesting that ED induced by LUTS was demonstrated both in a basic animal study and human epidemiologic study.

In this study, we conducted the initial examination to elucidate the prevalence of ED and LUTS. After 15 years, a follow-up examination was conducted to determine the changes of sexual function and LUTS. A 15-year longitudinal analysis is long enough to evaluate the natural histories of ED and LUTS. The goal of this study was to clarify the onset sequence for ED and LUTS and determine whether the variables of LUTS or ED could be predictors for the onset of the other using the long-term longitudinal data of a community-based study. Our data showed that there were more men with prior onset of LUTS than men with prior onset of ED among those with both ED and LUTS in this long-term longitudinal study. Moreover, we found that nighttime frequency of 2 or more times was a significant predictor for the onset of ED.

We could not clarify the connection between nocturia and subsequent ED. We recognized only the phenomenon that there

were more men with prior onset of nocturia. Several reports have hypothesized a link between LUTS and ED. Both storage symptoms, including nocturia, and ED have many risk factors. Previous reports suggested that the pathophysiology of storage LUTS included metabolic factors, pelvis ischemia, chronic prostatic inflammation, and associated comorbidities.<sup>25</sup> One or more of these factors may be leading factors for prior-onset nocturia. For example, one hypothesis for the mechanism linking LUTS with ED includes the prostate and ischemia. Clinical studies have shown that bladder and prostate blood flows decrease with aging.<sup>26</sup> In a case-control study, it was found that the frequency of nighttime micturition negatively correlated with bladder perfusion evaluated by transrectal color Doppler ultrasonography.<sup>27,28</sup> Therefore, pelvic ischemia may be one mechanism via which nocturia is a predictor for ED with aging.

This longitudinal study had several limitations. The major one is the small number of men enrolled in the survey. Therefore, our results are only confirmation of the phenomenon in a small cohort. However, to our knowledge, there is no existing report that ranks with the present study cohort in Japan.<sup>5</sup> Another limitation is that our survey included only 2 assessment periods. Our epidemiologic survey was conducted only 2 times, in 1992 and 2007. If we had more data, including midpoint assessments for more participants, our results would be more reliable.

Another one is that we do not have data for testosterone levels and body mass index, both of which are suggested to have associations with LUTS and ED. We need to conduct further study including the data on both to further clarify the onset sequences for ED<sup>29</sup> and LUTS.<sup>30</sup>

In this study, we found that patients with nighttime frequency of 2 times or more tended to develop ED. However, it has not been clarified whether treatment for nocturia can prevent the onset of ED. Further study should be performed prospectively to determine the relation between treatment for nocturia and the onset of ED.

## CONCLUSIONS

We investigated which condition and symptoms developed before the other one and which variables of LUTS or ED predicted the onset of the other in a longitudinal community-based

study. Although our study sample size was small, there were more men with prior onset of LUTS, especially nocturia, than men with prior onset of ED among those with both ED and LUTS in this long-term longitudinal study. Nocturia may be a predictor of subsequent ED.

**Corresponding Author:** Ko Kobayashi, MD, PhD, Department of Urology, Sapporo Medical University School of Medicine S1W16, Chuo-ku, Sapporo 060-8543, Japan. Tel: 81-(0)11-611-2111 ext. 34720; Fax: 81-(0)11-612-2709; E-mail: [kou@sapmed.ac.jp](mailto:kou@sapmed.ac.jp)

*Conflict of Interest:* The authors report no conflicts of interest.

*Funding:* None.

## STATEMENT OF AUTHORSHIP

Yohei Matsuda, Formal Analysis, Writing - Original Draft; Ko Kobayashi, Formal Analysis, Investigation, Validation, Writing - Review & Editing; Fumimasa Fukuta, Data Curation; Akio Takayanagi, Project Administration; Kohei Hashimoto, Project Administration; Toshiaki Tanaka, Supervision; Naoya Masumori, Investigation, Supervision.

## REFERENCES

- Rosen R, Altwein J, Boyle P, et al. Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7). *Eur Urol* 2003; **44**:637-649.
- Nakamura M, Fujimura T, Nagata M, et al. Association between lower urinary tract symptoms and sexual dysfunction assessed using the core lower urinary tract symptom score and International Index of Erectile Function-5 questionnaires. *Aging Male* 2012; **15**:111-114.
- Ponholzer A, Temml C, Obermayr R, et al. Association between lower urinary tract symptoms and erectile dysfunction. *Urology* 2004; **64**:772-776.
- [4]. Svatikova A, Kopecky SL. Why and how cardiovascular Screening should be Implemented in sexual medicine practice: erectile dysfunction and cardiovascular disease. *J Sex Med* 2020; **17**:1045-1048.
- Masumori N, Tsukamoto T, Kumamoto Y, et al. Decline of sexual function with age in Japanese men compared with American men—Results of two community-based studies. *Urology* 1999; **54**:335-344.
- Fukuta F, Masumori N, Mori M, et al. Natural history of lower urinary tract symptoms in Japanese men from a 15-year longitudinal community-based study. *BJU Int* 2012; **110**:1023-1029.
- Matsuda Y, Hisasue S, Kumamoto Y, et al. Correlation between erection Hardness score and Nocturnal penile Tumescence Measurement. *J Sex Med* 2014; **11**:2272-2276.
- Takayanagi A, Kobayashi K, Fukuta F, et al. Changes of sexual function and perception in Japanese men: a 15-year cross-sectional community-based study. *Int J Urol* 2016; **23**:941-945.
- Homma Y, Tsukamoto T, Yasuda K, et al. Linguistic validation of Japanese version of international prostate symptom score and BPH impact index. *Nihon Hinyokika Gakkai Zasshi* 2002; **93**:669-680; Japanese.
- Masumori N, Tsukamoto T, Kumamoto Y, et al. Japanese men have smaller prostate volumes but comparable urinary flow rates relative to American men: results of community based studies in 2 countries. *J Urol* 1996; **155**:1324-1327.
- Masumori N, Tsukamoto T, Kumamoto Y, et al. Age-related differences in internal prostatic architecture on transrectal ultrasonography: results of a community based survey in Japan. *J Urol* 1997; **157**:1718-1722.
- Fukuta F, Masumori N, Mori M, et al. Internal prostatic architecture on transrectal ultrasonography predicts future prostatic growth: natural history of prostatic hyperplasia in a 15-year longitudinal community-based study. *Prostate* 2011; **71**:597-603.
- Fukuta F, Masumori N, Mori M, et al. Incidence and risk of treatment for benign prostatic hyperplasia in Japanese men: a 15-year longitudinal community-based study. *Int J Urol* 2013; **20**:100-106.
- World Health Organization. Health statistics and information systems. Available at: <https://www.who.int/healthinfo/survey/ageingdefnolder/en/>.
- Wein AJ, Coyne KS, Tubaro A, et al. The impact of lower urinary tract symptoms on male sexual health: EpiLUTS. *BJU Int* 2009; **103**(Suppl 3):33-41.
- Brookes ST, Link CL, Donovan JL, et al. Relationship between lower urinary tract symptoms and erectile dysfunction: results from the Boston Area Community Health Survey. *J Urol* 2008; **179**:250-255.
- Jeong HC, Kim SU, Lee WC, et al. Sexual behavior of the elderly in urban areas. *World J Mens Health* 2012; **30**:166-171.
- Braun MH, Sommer F, Haupt G, et al. Lower urinary tract symptoms and erectile dysfunction: co-morbidity or typical "Aging Male" symptoms? Results of the "Cologne Male Survey". *Eur Urol* 2003; **44**:588-594.
- Terai A, Ichioka K, Matsui Y, et al. Association of lower urinary tract symptoms with erectile dysfunction in Japanese men. *Urology* 2004; **64**:132-136.
- Shiri R, Häkkinen JT, Hakama M, et al. Effect of lower urinary tract symptoms on the incidence of erectile dysfunction. *J Urol* 2005; **174**:205-209.
- Gacci M, Eardley I, Giuliano F, et al. Critical analysis of the relationship between sexual dysfunctions and lower urinary tract symptoms due to benign prostatic hyperplasia. *Eur Urol* 2011; **60**:809-825.
- Nasir AR, Zehri AA, Abbas F, et al. The correlation between international prostate symptoms score and sexual health inventory in men with lower urinary tract symptoms. *Int Urol Nephrol* 2011; **43**:625-629.
- Fwu CW, Kirkali Z, McVary KT, et al. Cross-sectional and longitudinal associations of sexual function with lower urinary



- tract symptoms in men with benign prostatic hyperplasia. *J Urol* 2015;193:231-238.
24. Kobayashi K, Kato R, Hisasue S, et al. Animal Model for the study of the relationship between lower urinary tract symptoms/bladder outlet obstruction and erectile dysfunction. *Int J Urol* 2011;18:710-715.
  25. Gacci M, Sebastianelli A, Spatafora P, et al. Best practice in the management of storage symptoms in male lower urinary tract symptoms: a review of the evidence base. *Ther Adv Urol* 2017;10:79-92.
  26. Thurmond P, Yang JH, Azadzi KM. LUTS in pelvic ischemia: a new concept in voiding dysfunction. *Am J Physiol Ren Physiol* 2016;310:F738-F743.
  27. Pinggera GM, Mitterberger M, Steiner E, et al. Association of lower urinary tract symptoms and chronic ischaemia of the lower urinary tract in elderly women and men: assessment using colour Doppler ultrasonography. *BJU Int* 2008;102:470-474.
  28. Nomiya M, Andersson KE, Yamaguchi O. Chronic bladder ischemia and oxidative stress: new pharmacotherapeutic targets for lower urinary tract symptoms. *Int J Urol* 2015;22:40-46.
  29. Kratzik CW, Schatzl G, Lunglmayr G, et al. The impact of age, body mass index and testosterone on erectile dysfunction. *J Urol* 2005;174:240-243.
  30. Shim JS, Kim JH, Yoon YS, et al. Serum testosterone levels are negatively correlated with international prostate symptom score and transitional prostate volume. *Low Urin Tract Symptoms* 2018;10:143-147.