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Association between Nocturnal Frequency and Erectile Function in Eugonadal Men with Benign Prostatic Obstruction: A Cross Sectional Study

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Purpose: We aimed to evaluate the association between nocturnal frequency and erectile dysfunction in patients with benign prostatic obstruction.

Materials and Methods: To evaluate the association, we simultaneous evaluated urodynamic study, prostate ultrasound, nocturnal tumescence test (nocturnal penile tumescence) for sleep-related erection (SRE) and two questionnaires, international prostate symptom score (IPSS) and 5-item version of the international index of erectile function (IIEF-5). Patients with hypogonadism or nocturnal polyuria were excluded.

Results: Forty-six patients were registered over 4 years. The mean age, prostate size, IPSS score, and IIEF-5 score were 67.65±5.51 years, 65.10±22.12 mL, 24.67±7.89, and 9.50±7.01, respectively. Among the IPSS subscores, nocturia was most significantly related to the total IIEF-5 score ($p<0.001$). More severe nocturia was associated with less frequent SRE ($p=0.003$) and shorter total duration of SRE ($p=0.002$), which in turn elucidated that nocturia was significantly related to the total amount of rigidity signals (rigidity activity unit, RAU) or tumescence signals (tumescence activity unit, TAU). Among objective urodynamic parameters, bladder compliance also correlated to RAU and TAU. Individual subjective erectile function (IIEF-5) was significantly related to both RAU and TAU.

Conclusions: Sleep fragmentation due to benign prostate obstruction related nocturnal frequency caused by reduced bladder compliance could decrease the frequency and duration of SRE, which decreases the total amount of SRE and reflects the patient's relevant erectile function.

Keywords: Erectile dysfunction; Nocturia; Prostate; Sleep

INTRODUCTION

Benign prostatic hyperplasia (BPH) is the most frequent disease in aging men, and the prevalence of BPH-related lower urinary tract symptoms (LUTS) increases with age [1]. Age-related prostatic tissue remodeling has been suggested as a mechanism of BPH development [2]. Enlarged prostate clogs the prostatic

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urethra and weakens the flow of urine to the bladder outlet. To overcome this, bladder wall thickening and remodeling occur [3]. This series of phenomena causes decreased bladder compliance and nocturia [4]. Blanker et al [5] defined clinical BPH as moderate to severe voiding symptoms (international prostate symptom score [IPSS] greater than 7 points) with prostate enlargement (volume greater than 30 mL) and decreased maximum urinary flow (less than 15 mL/s), and they found that clinical BPH is an independent risk factor for nocturia.

Several reports have suggested that BPH-related nocturia could be associated with erectile function [6,7], whereas there are opposite opinions [8,9]. With regard to the nocturia, nocturnal polyuria rather than benign prostatic obstruction (BPO) accounts for a greater proportion of nocturia [10]. In addition, the serum testosterone level not only exerts an influence on the LUTS but also affect sexual function [11,12]. In these reasons, to investigate the relationship between pure BPO related nocturia and erectile function, researchers should narrow their indication by excluding the other causative factors. Herein, we aimed to evaluate whether BPH related LUTS was related to erectile function in eugonadal men.

MATERIALS AND METHODS

1. Patient selection

This study was prospectively conducted with consecutive patients between September 2014 and August 2018. For registration, all patients had to meet all of the following inclusion criteria: 1) moderate to severe LUTS on the IPSS questionnaire as suggested by previous research [5]; 2) prostate size over 30 mL on ultrasonography; and 3) urodynamically proven bladder outlet obstruction (BOO) (BOO index of 40 or more). In cases where the above conditions were satisfied, BPO was considered. Patients with one of the following were excluded from the study: 1) patients aged over 80 years; 2) patients with hypogonadism (testosterone less than 3.0 ng/mL); 3) patients with nocturnal urine volume over 30% of the total urine volume on the frequency-volume chart; 4) patients with documented prostate cancer; 5) patients with any history or ongoing treatment of pelvic cavity malignancy, such as bladder cancer or rectosigmoid cancer; 6) patients with a history of spinal cord disease, such as myelopathy; 7) uncontrolled diabetes (HbA1c>7) [13]; 8) uncontrolled hypertension (HTN) (systolic blood pressure [bp]>140 or diastolic bp>90 with medication) [14]; 9) patients with any sleep disorder such as insomnia or obstructive sleep apnea; and 10) patients with current phosphodiesterase type 5 inhibitor users.

2. Measurements and study process

To select patients who complained of LUTS due to BPH, we performed transrectal ultrasonography and urodynamic studies (invasive urodynamic test and non-invasive uroflowmetery) before enrollment as described above. Invasive urodynamic test was performed using a 2-way 8-French catheter (Peters Surgical, Bobigny, France) inserted into the bladder *via* the urethra. The catheter was used to infuse isotonic saline (at 40 mL/min at room temperature) and to record the vesical pressure. An abdominal pressure measurement was recorded using a catheter with a PVC balloon placed in the rectum (Peters Surgical). The detrusor pressure at the maximum flow rate (PdetQmax) was measured during the pressure flow study (voiding phase), from which the bladder contractility index (Pdetmax+5xQmax) and the BOO index (Pdetmax-2xQmax) were calculated. For non-invasive uroflowmetry, patients voided freely without catheterization. At that time, we measured and recorded the Qmax and postvoid residual urine volume (PVR). The PVR was measured using a Biocon 500 ultrasound scanner (Medline Industries, Inc., Mundelein, IL, USA).

In addition, the nocturnal penile tumescence (NPT) test and two questionnaires, the IPSS [15] and 5-item version of the international index of erectile function (IIEF-5) [16], were applied. NPT testing was performed twice using the RigiScan-Plus TM software, ver. 5.2 (Dacomed, Minneapolis, MN, USA). Better one from two day results was employed for analysis of nocturnal erectile function. Rigidity activity unit (RAU) and tumescence activity unit (TAU) were evaluated at both penile tip and penile base. The frequency and duration of sleep-related erection (SRE) were also checked [17].

With aforementioned measurements, we investigated the relationship between 1) symptoms related to LUTS (IPSS) and symtoms related to erectile function (IIEF-5), 2) nocturia (subjective symptom from IPSS questionnaire) and NPT parameters, 3) objective urodynamic parameters and NPT parameters, and 4) IIEF-5 scores and NPT parameters.

3. Statistical analysis

For correlation between two variables, Spearman's test was used; to investigate the linearity between two variables, we used linear regression analysis. It was considered statistically significant when p-value was less than 0.05. Using G*Power 3.1, target sample size (n=44) was calculated with effect size 0.4, α=0.05 and β=0.2 under correlation model.

4. Ethics statement

The St. Vincent's Hospital, The Catholic University of Korea, Institutional Review Board approved the observational study design and access to the patients' medical records (approval number: VC13OISI0222, date of approval: February 26th, 2014). This study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants in the study.

RESULTS

Forty-six patients were finally enrolled in the study. The mean age, prostate size, IPSS score, and IIEF-5 score were 67.65±5.51 years, 65.10±22.12 mL, 24.67±7.89, and 9.50±7.01, respectively. The patients' characteristics are described in Table 1.

Considering LUTS among the 46 enrolled patients, 35 patients had severe symptoms (IPSS score 19–35), and the other 11 patents had moderate symptoms (IPSS score 8–19). With regard to subjective erectile function, 21 of the 46 patients had severe erectile dysfunction (ED) (IIEF-5 score less than 8), 5 had moderate ED (IIEF-5 score 8~11), 19 had mild ED (IIEF-5 score 12~21), and 1 had normal erectile function (IIEF-5 score more than 21).

The total IPSS score was significantly correlated with the total IIEF-5 score (p=0.013, Spearman's rho=-0.363). Among the IPSS subscores, item number 7, indicating 'the frequency of nocturia', was most significantly related to the total IIEF-5 score (p<0.001, Spearman's rho=-0.548) (Table 2). When we considered other parameters, diabetes mellitus and BOO index were significantly associated with total IIEF-5 score. Multivariate analysis showed the frequency of nocturia and underlying diabetes mellitus were two leading causative risk factor in BPO patients.

NPT test was failed in 8 patients. Those eight patients did not want the test because they felt bothersome to keep the tight ring type sensors on their penis, especially when they urinated. When we evaluated

Table 1. Patients' characteristics

Characteristic	Value
Subject	46 (100)
Age (y)	67.65±5.51
BMI (kg/m^2)	24.76±2.87
Diabetes (%)	15 (32.6)
Hypertension (%)	15 (32.6)
Smoking (%)[a]	5 (10.9)
Nocturia (%) in FVC	18.70±7.34
Prostate size (mL)	65.10±22.12
PSA (ng/mL)	4.93±4.37
Testosterone (ng/mL)	3.79±0.83
IPSS	24.67±7.89
IPSS-1	3.52±1.59
IPSS-2	3.74±1.47
IPSS-3	3.74±1.39
IPSS-4	2.98±1.78
IPSS-5	4.17±1.10
IPSS-6	3.41±1.67
IPSS-7	3.13±1.36
IIEF	9.50±7.01
IIEF-1	2.22±1.13
IIEF-2	1.70±1.41
IIEF-3	1.76±1.48
IIEF-4	2.07±1.84
IIEF-5	1.76±1.58
Urodynamic parameters	
Qmax (mL/s)	7.56±2.95
Voiding volume (mL)	221.17±94.00
Postvoid residual volume (mL)	124.15±82.81
Bladder compliance (mL/cmH_2O)	60.20±25.82
Bladder outlet obstruction index	65.59±27.06
Bladder contractility index	101.05±32.99
NPT test (n=38)	
Frequency of SRE	2.42±1.22
Total duration of event (h)	0.68±0.53
RAU tip	20.55±16.33
TAU tip	9.90±7.38
RAU base	22.21±16.14
TAU base	13.11±10.77

Values are presented as number (%) or mean±standard deviation.
BMI: body mass index, FVC: frequency-volume chart, PSA: prostate specific antigen, IPSS: international prostate symptom score, IIEF: international index of erectile function, Qmax: maximum flow rate, NPT: nocturnal penile tumescence, SRE: sleep related erection, RAU: rigidity activity unit, TAU: tumescence activity unit.
[a]We applied smoking history for over 20 pack-years as a risk factor for erectile dysfunction [18].

Table 2. The correlation between IIEF score and other baseline parameters (n=46)

Variable	Data
Spearman's correlation[a]	
IPSS total	-0.363, 0.013
IPSS-1	-0.351, 0.017
IPSS-2	-0.152, 0.314
IPSS-3	-0.287, 0.053
IPSS-4	-0.161, 0.285
IPSS-5	-0.224, 0.134
IPSS-6	-0.212, 0.157
IPSS-7	-0.548, <0.001
Age	0.071, 0.639
BMI	0.068, 0.654
Diabetes mellitus	-0.409, 0.005
Hypertension	-0.018, 0.908
Smoking	-0.034, 0.821
Testosterone	-0.049, 0.744
Prostate size	0.219, 0.143
Qmax	0.037, 0.805
Voiding volume	0.107, 0.478
Postvoid residual urine	-0.031, 0.839
Bladder compliance	0.248, 0.096
Bladder outlet obstruction index	0.293, 0.048
Bladder contractility index	0.265, 0.075
Multivariate regression analysis[b]	
IPSS-1	0.659, -1.423–2.226
IPSS-3	0.221, -3.078–0.734
IPSS-7	0.003, -3.993–-0.858
Diabetes mellitus	0.004, -8.942–-1.821
Bladder compliance	0.572, -0.055–0.099
Bladder outlet obstruction index	0.595, -0.081–0.138
Bladder contractility index	0.495, -0.062–0.125

IIEF: international index of erectile function, IPSS: international prostate symptom score, BMI: body mass index, Qmax: maximum flow rate.
[a]Data were presented with Spearman's rho and p-value.
[b]Data were presented with p-value and 95% confidential interval for beta coefficient.

thirty-eight patients with measurable signals following the NPT test more severe nocturia was associated with less frequent SRE (p=0.003, R^2=0.217) and total duration of SRE (p=0.002, R^2=0.244), which in turn elucidated that nocturia was significantly related to the total amount (integral) of rigidity signals (RAU) or tumescence signals (TAU) (Fig. 1).

Correlation between urodynamic parameters and NPT parameters was also evaluated. We could find that bladder compliance was significantly related to some of NPT parameters which indicated that BPO related bladder storage dysfunction was associated with total SRE duration and/or frequency, which is in the same line with the results from the correlation test between nocturia (IPSS-7) and NPT test (Table 3).

Individual subjective erectile symptoms (IIEF-5) were significantly related to both RAU and TAU (Table 4). Because parameters such as RAU (tip/base) and TAU (tip/base) had high multicollinearity for one another (variance inflation factors against IIEF-5 were 10.40/7.98 and 9.11/6.87, respectively), we used stepwise multiple regression test, then RAU in penile tip was revealed as the most significant parameter in association with total IIEF-5 score (p=0.001, 0.104<95% confidence interval<0.346). These results strengthen a hypothesis that a reduced total duration of SRE due to nocturnal frequency could be reflected in the subjective erectile symptoms. Looking the Fig. 2, maximal rigidity is similar among 3 patients, however total amount of rigidity (RAU) was much larger in A than B/C, which might be due to the number of sleep fragmentation caused by nocturia.

In the present cohort, diabetes mellitus was a risk factor for subjective erectile function whereas age, BMI, HTN, and smoking [18] did not significantly influenced on the IIEF score (p-values were 0.639, 0.654, 0.908, and 0.821, respectively) (Table 2). The reason might be that 1) age distribution was very narrow because all enrolled patients had moderate to severe LUTS with BPO, 2) BMI distribution was also very narrow without significant obese patients, 3) all patients with HTN were under well control, and 4) only 5 patients were smokers in this cohort.

DISCUSSION

Nocturia is the most bothersome symptom among LUTS [19,20], and the frequency of nocturia seems to be significantly associated with poor sleep quality [21]. The negative effects of nocturia include sleep fragmentation [22], which typically refers to brief arousals that occur during a sleep period [23]. Furthermore, it has been suggested that SRE could be important to maintain erectile function [24]; thus, the long-term effect of nocturia, which exerts a great influence on sleep quality [25], may gradually decrease erectile function by disturbing SRE. In patients with BPO, we found that LUTS, especially the frequency of nocturia, were significantly associated with erectile function and the

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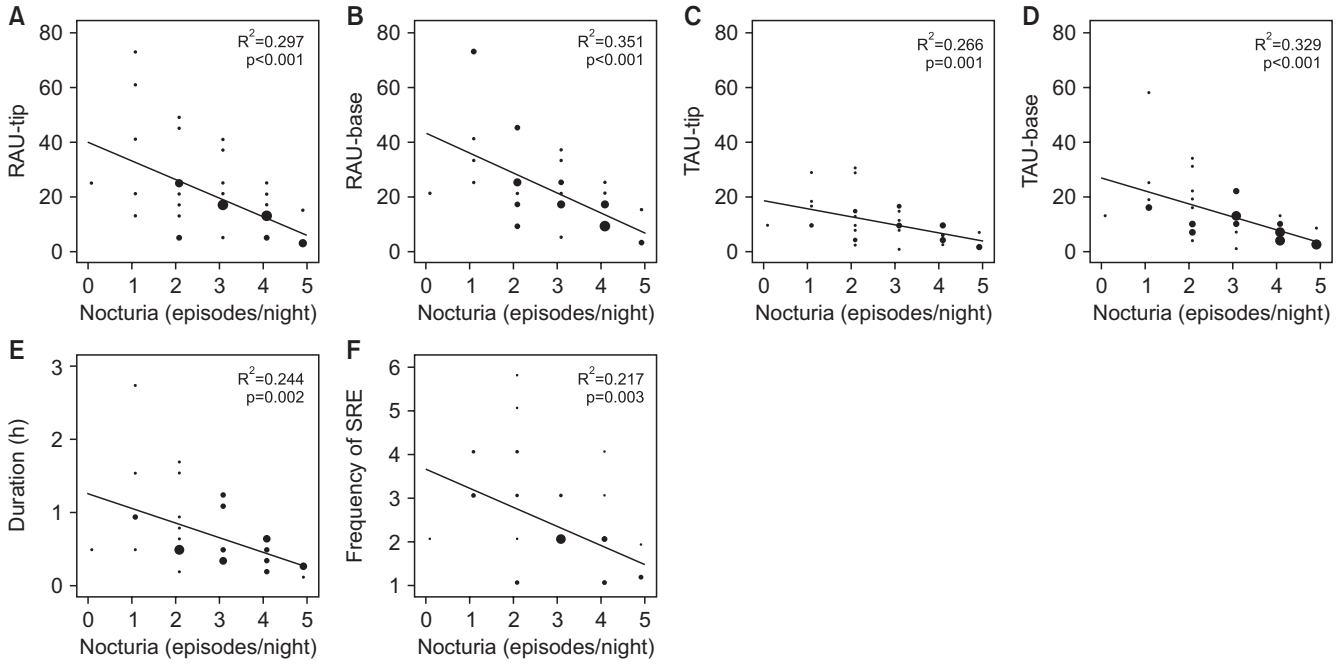

Fig. 1. Relationship between nocturnal penile tumescence parameters and nocturia (n=38). (A–D) Total amount of rigidity activity unit (RAU) and tumescence activity unit (TAU) were inversely correlated with nocturia. (E, F) Total duration and the frequency of sleep-related erection (SRE) were inversely correlated with the frequency of nocturia.

Table 3. The correlation between urodynamic parameters and NPT parameters (n=38)

	RAU tip	TAU tip	RAU base	TAU base
Qmax				
Spearman's rho	0.121	0.090	0.189	0.162
p-value	0.468	0.590	0.255	0.331
VV				
Spearman's rho	-0.037	-0.034	0.046	0.062
p-value	0.825	0.838	0.786	0.713
PVR				
Spearman's rho	0.207	0.278	0.278	0.173
p-value	0.212	0.091	0.092	0.298
Compliance				
Spearman's rho	0.304	0.283	0.349	0.326
p-value	0.064	0.085	0.032	0.046
BOOI				
Spearman's rho	0.186	0.260	0.135	0.078
p-value	0.262	0.115	0.420	0.641
BCI				
Spearman's rho	0.132	0.128	0.103	0.040
p-value	0.429	0.443	0.538	0.811

NPT: nocturnal penile tumescence, RAU: rigidity activity unit, TAU: tumescence activity unit, Qmax: maximum flow rate, VV: voiding volume, PVR: postvoid residual volume, Compliance: bladder compliance, BOOI: bladder outlet obstruction index, BCI: bladder contractility index.

total amount of SRE (Table 2, Fig. 1).

With regard to hormonal effects, it is well known that sleep deprivation is responsible for hypogonadotropic hypogonadism [26]. Because testosterone is mainly secreted during sleep in response to luteinizing hormone pulse initiation [27], which is strengthened by rapid eye movement (REM) sleep [28], it was important to check testosterone levels to exclude the effect of

hypogonadism on ED. In our study, testosterone levels were 3.0 ng/mL or more (mean, 3.79 ng/mL). At this point, we should be aware of the different effects on sex hormones between sleep fragmentation and REM sleep deprivation. Luboshitzky et al [29] showed that fragmented sleep disrupted the testosterone rhythm with a considerable attenuation of the nocturnal rise only in subjects who did not show REM sleep, and the authors emphasized the appearance of first REM sleep in association with the sleep-related rise in testosterone. Therefore, the patients (eugonadal) in the present study might have experienced one or more intact REM sleep cycles or several partially disturbed REM sleep cycles (not REM deprivation). Considering that the amount of SRE was significantly less in patients with moderate to severe nocturia (due to a reduced duration and frequency of SRE), the total amount of REM sleep might be more disturbed in patients with moderate to severe nocturia than in patients with mild nocturia. For a more comprehensive and definite demonstration of the effect of nocturia on SRE, further studies concomitantly using the NPT and polysomnography (or a relevant modality to check REM sleep) would be required.

Table 4. The correlation between IIEF score and NPT parameters (n=38)

	p-value	Spearman's rho
RAU[a] tip	<0.001	0.639
TAU tip	0.001	0.536
RAU base	0.007	0.432
TAU base	0.007	0.431
Time	0.036	0.341
Event	0.078	0.289

IIEF: international index of erectile function, NPT: nocturnal penile tumescence, RAU: rigidity activity unit, TAU: tumescence activity unit, Time: the duration of total sleep related erection, Event: the frequency of sleep related erection.
[a]Using stepwise multiple regression analysis, RAU in penile tip showed the most significant parameter in association with IIEF score (p=0.001, 0.104<95% confidence interval<0.346).

Over two-thirds of the blood supply and subsequent exchange of metabolites in the cavernosal tissue occur during SRE [24]. Chronic disturbance of SRE may be an important factor for the development and progression of ED. Based on our results, individual erectile function was reflected by the total amount of SRE (RAU and TAU) where total amount of SRE in penile tip (RAU) was the most important parameter reflect-

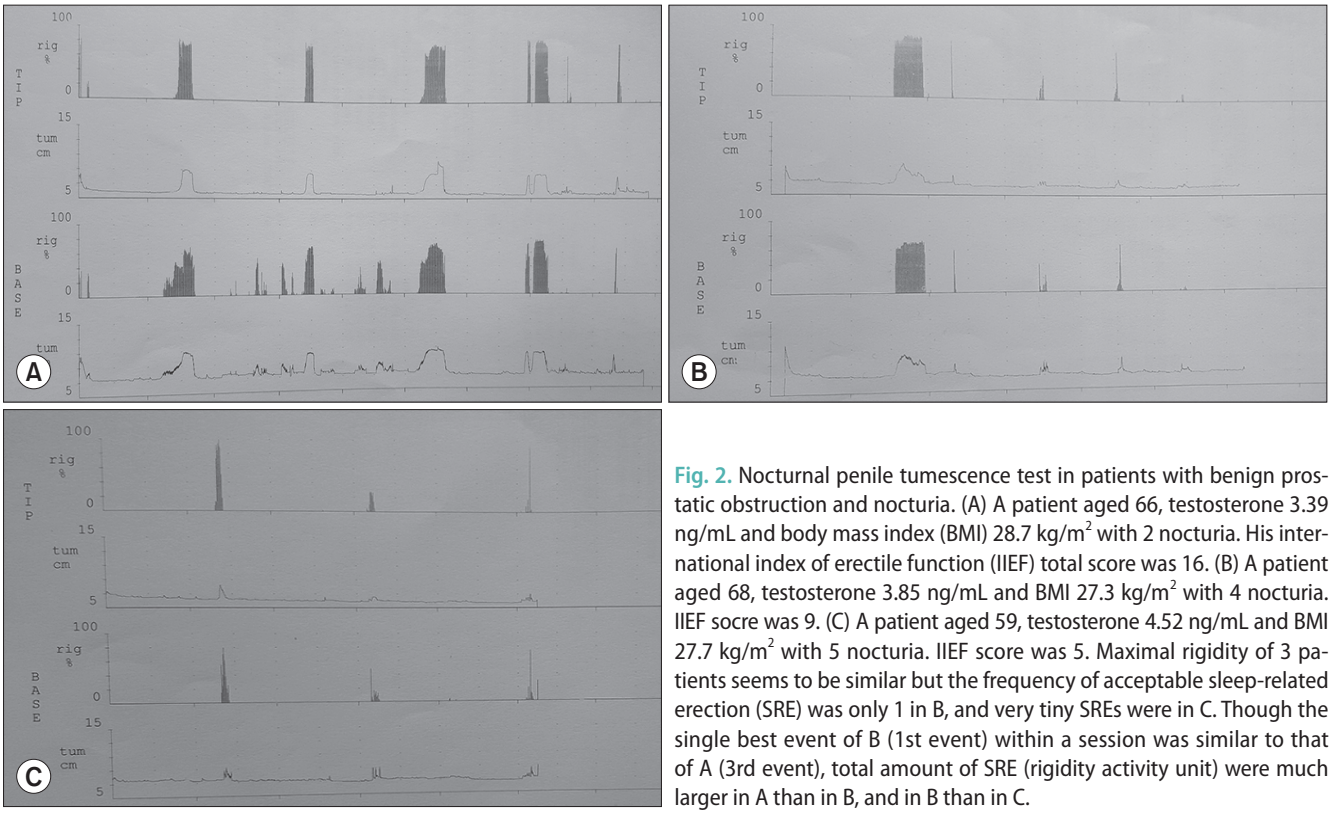

Fig. 2. Nocturnal penile tumescence test in patients with benign prostatic obstruction and nocturia. (A) A patient aged 66, testosterone 3.39 ng/mL and body mass index (BMI) 28.7 kg/m^2 with 2 nocturia. His international index of erectile function (IIEF) total score was 16. (B) A patient aged 68, testosterone 3.85 ng/mL and BMI 27.3 kg/m^2 with 4 nocturia. IIEF socre was 9. (C) A patient aged 59, testosterone 4.52 ng/mL and BMI 27.7 kg/m^2 with 5 nocturia. IIEF score was 5. Maximal rigidity of 3 patients seems to be similar but the frequency of acceptable sleep-related erection (SRE) was only 1 in B, and very tiny SREs were in C. Though the single best event of B (1st event) within a session was similar to that of A (3rd event), total amount of SRE (rigidity activity unit) were much larger in A than in B, and in B than in C.

ing the individual erectile function (Table 4). Thus, both the loss of the frequency of SRE and the shortening of the duration of SRE are important for individual erectile function.

It is interesting that IPSS-7 was inversely correlated to SRE in the present study (Fig. 1). IPSS-7 and SRE have a common feature that they reflect night-time event connected to sleep event. In the present study, we could find an association between bladder compliance and the total amount of SRE. Therefore, we could assume that BPO related nocturia due to decreased bladder compliance not only decreases total amount of SRE but also exerts an influence on the subjective erectile function.

ED has multifactorial causes and is a phenomenon resulting from many morbidities [30]; thus, the progression of ED generally requires a long-term period. Therefore, erectile function may not be enhanced right after the improvement of nocturia in elderly patients with BPH. However, several studies showed improvement in both nocturia and erectile function after the management of nocturnal frequency in clinically suspected BPO patients [6,7]. Therefore, a large population-based, long-term prospective study with narrow inclusive criteria is warranted to determine whether early control of nocturnal frequency could be a preventive method against ED progression.

The major limitation of the present study was the small sample size. Because of the narrow indications of the present study that include BPO conditions (confirmed by urodynamic study, transrectal ultrasound, and moderate to severe IPSS score) and exclude nocturnal polyuria, hypogonadism, and sleep disorders, we could enroll only 46 patients over 4 years.

CONCLUSIONS

Nocturnal frequency due to BPO was significantly associated with erectile function. Sleep fragmentation by nocturnal frequency due to decreased bladder compliance might have an association with the decreased amount of SRE in eugonadal BPO patients, which may reflect individual erectile function.

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Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: DSL, SWK, DWS. Data curation: DSL, DWS. Formal analysis: DSL. Investigation: DSL. Methodology: DSL. Supervision: SWK. Writing – original draft: DSL. Writing – review & editing: SWK, DWS.

Data Sharing Statement

The data analyzed for this study have been deposited in HARVARD Dataverse and are available at https://doi.org/10.7910/DVN/XFXZPW.

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