INTRODUCTION

Recently, an association between erectile dysfunction (ED) and lower urinary tract symptoms (LUTS) has been suggested in some clinical studies.²⁻⁴ 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.¹ This study revealed that the presence and severity of LUTS were risk factors for sexual disorders in aging males.¹ Similarly, some studies demonstrated the relationship between the variables of LUTS (voiding symptoms, nocturia and quality of life [QOL] score) and erectile function.²⁻³

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.⁴ 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
The 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 and 2007. 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. 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. 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), QOL index, and prostate volume (PV).

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 ≥ 60 years, total IPSS ≥ 8, individual IPSS ≥ 2, QOL index ≥ 2, and PV ≥ 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. The cutoff point of the PV used the average PV in Japanese. 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).

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

| Table 1. Participant characteristics |
|-------------------------------------|
| Variables                   | Initial study | Follow-up study | P value |
|------------------------------|--------------|----------------|---------|
| Age (years)                 | 57           | 71             | <0.01   |
| Total IPSS                   | 7            | 9              | 0.01    |
| IPSS 1 (not empty)          | 1            | 1              | 0.81    |
| IPSS 2 (day frequency)      | 1            | 1              | 0.67    |
| IPSS 3 (stop/start)         | 0            | 1              | 0.70    |
| IPSS 4 (urgency)            | 1            | 1              | 0.07    |
| IPSS 5 (weak stream)        | 1            | 1              | 0.01    |
| IPSS 6 (straining)          | 1            | 1              | 0.50    |
| IPSS 7 (nocturia)           | 1            | 1              | <0.01   |
| QOL score                   | 2            | 2              | 0.02    |
| PV (mL)                     | 17.7         | 24.3           | <0.01   |
| Erectile rigidity score     | 5            | 2              | <0.01   |

ED = erectile dysfunction; IPSS = International Prostate Symptom Score; PV = prostate volume; QOL = quality of life.
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 (+)  | LUTS (-)/ED (-)  |
| n = 47           | n = 9 (19.1%)     |
| LUTS (+)/ED (-)  | LUTS (-)/ED (-)  |
| n = 16 (34.0%)   | n = 16 (34.0%)    |
| LUTS (+)/ED (+)  | LUTS (-)/ED (+)  |
| n = 6 (12.8%)    | n = 5 (13.2%)     |
| LUTS (+)/ED (+)  | LUTS (+)/ED (+)  |
| n = 16 (34.0%)   | n = 15 (39.5%)    |

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, 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 ≥ 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 and surveys of patients with benign prostatic hyperplasia/LUTS 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
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),

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. 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. 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. 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. 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. 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 and LUTS.

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

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**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 | P-value | Univariate analysis | Multivariable analysis |
|-------------------------|--------|---------|---------------------|------------------------|
| Total IPSS              | ≥8     | .05     |                     |                        |
| Nighttime frequency     | ≥2     | <.01    |                     |                        |
| PV (mL)                 | ≥20    | .05     |                     |                        |
| Age (years)             | ≥60    | <.01    | 7.10 2.09—24.13 .01 |                        |
| Nocturia (IPSS Q7)      | ≥2     | <.01    | 1.50 0.46—4.97 .51  |                        |
| QOL index               | ≥2     | <.05    | 15.83 3.05—82.15 .01|                        |
| PV (mL)                 | ≥20    | .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.
Which happens earlier, LUTS or ED?

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.

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