

# Nocturia and prevalence of erectile dysfunction in Japanese patients with type 2 diabetes mellitus: The Dogo Study

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## Keywords

Diabetes, Erectile dysfunction, Nocturia

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## ABSTRACT

**Aims/Introduction:** Several epidemiological studies have reported a positive association between nocturia and erectile dysfunction (ED). Yet only limited evidence exists regarding the association between nocturia and ED among patients with type 2 diabetes mellitus, although nocturia and ED are common among type 2 diabetes mellitus patients.

**Material and Methods:** Study participants were 332 male Japanese patients with type 2 diabetes mellitus, aged 19–70 years, who had undergone blood tests at our institutions. A self-administered questionnaire was used to collect information on the variables under study. Adjustment was made for age, body mass index, hypertension, stroke, ischemic heart disease, glycosylated hemoglobin and diabetic neuropathy. ED, moderate to severe ED and severe ED were defined as present when a participant had a Sexual Health Inventory for Men score <22, <12 and <8, respectively. Study participants were considered to have nocturia if they answered ‘once or more’ to the question: ‘Within 1 week, how many times do you typically wake up to urinate from sleeping at night until waking in the morning?’

**Results:** The prevalence of nocturia was 79.8%. Nocturia was independently positively associated with ED and moderate to severe ED: the adjusted odds ratios were 7.86 (95% confidence interval 2.11–33.56) and 2.17 (95% confidence interval 1.16–4.12), respectively. The positive association between nocturia and severe ED fell just short of significance.

**Conclusions:** In Japanese men with type 2 diabetes mellitus, nocturia might be associated with ED and moderate to severe ED.

## INTRODUCTION

The International Continence Society defines nocturia as the condition of waking up to void once or more during a typical night<sup>1</sup>. The prevalence of nocturia is higher among patients with diabetes mellitus than among those without<sup>2–7</sup>. Similarly, the prevalence of erectile dysfunction (ED) is higher among patients with diabetes mellitus than among those without<sup>8</sup>.

In non-diabetic populations, nocturia was cross-sectionally associated with ED in a USA community-based study of 2,301 men<sup>9</sup>, a Malaysian study of 353 men<sup>10</sup>, a Korean study of 365 men with benign hyperplasia<sup>11</sup>, and two Japanese studies of 2,084 men<sup>12</sup> and 220 men<sup>13</sup>. To our knowledge, however, only one epidemiological study has reported on the relationship between nocturia and ED among a diabetic population; in that study, which examined 453 Taiwanese men with type 2 diabetes mellitus, nocturia was significantly positively associated

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with ED<sup>14</sup>. Thus, we aimed to evaluate the relationship between nocturia and ED among Japanese patients with type 2 diabetes mellitus.

## MATERIALS AND METHODS

### Study population

The Dogo Study is a multicenter prospective cohort study that has recruited 1,051 Japanese patients with previously diagnosed type 2 diabetes mellitus from September 2009 to September 2014 (median age at recruitment 61.6 years; range 19–88 years; 60.9% men). Collaborating physicians from 10 hospitals who specialize in diabetes mellitus were responsible for the diagnoses of type 2 diabetes mellitus, according to the Japan Diabetes Society criteria.

Excluded from our current analysis were 719 patients because of female sex or incomplete data on the variables under study. Thus, the final analysis sample consisted of 332 patients. The present study protocol received ethical approval from the institutional review board of Ehime University Graduate School of Medicine. Written informed consent was obtained from all patients enrolled in the Dogo Study.

### Measurements

Each participant completed a self-administered questionnaire, which collected data on diabetes duration, current smoking habits, current drinking habits, use of antihypertensive medication, use of antihyperlipidemic medication, height and weight. Each patient's body mass index was calculated as their weight (kg) divided by the square of their height (m<sup>2</sup>). Current smoking was defined as positive if a study participant reported smoking at least one cigarette per day. Blood pressure was measured with a cuff in the sitting position, after a rest period of greater than 5 min. Hypertension was defined as positive if systolic blood pressure was >140 mmHg, diastolic blood pressure was >90 mmHg, or both, or if the patient had received antihypertensive medication. Dyslipidemia was defined as positive if serum total cholesterol concentration was >220 mg/dL, triglyceride concentration was >150 mg/dL or high-density lipoprotein cholesterol concentration was <40 mg/dL, or if the patients were already being treated with lipid-lowering agents. Stroke and ischemic heart disease were assessed based on the self-administered questionnaires, medical records and/or admission data. Use of insulin and oral antihyperglycemic agents were based on medical records.

### Assessment of nocturia

Study participants were considered to have nocturia if they answered 'once or more' to the question: 'How many times do you typically wake up to urinate from sleeping at night until waking in the morning?'

### Assessment of erectile dysfunction

The Sexual Health Inventory for Men (SHIM) is a validated abridged five-item version of the 15-item International Index of Erectile Function questionnaire. With a total score ranging

from 1 to 25, the degree of ED was classified into the following five categories: severe (1–7), moderate (8–11), mild to moderate (12–16), mild (17–21) and no ED (22–25)<sup>15</sup>. In the present study, we used the following three outcomes: (i) ED was defined as present when a participant had a SHIM score <22; (ii) moderate to severe ED was defined as present when a participant had a SHIM score <12; and (iii) severe ED was defined as present when a participant had a SHIM score <8.

### Assessing the complications of type 2 diabetes mellitus

Microvascular complications of type 2 diabetes mellitus included retinopathy, nephropathy and neuropathy. Retinopathy was diagnosed based on the presence of hemorrhage, microaneurysm, soft and hard exudates, areas of neovascularization or laser coagulation scars in at least one eye. Diagnosis was carried out using fluorescence funduscopy on dilated pupils within 3 months of recruitment. Several ophthalmology specialists were responsible for evaluating the participants' fundi, and all ophthalmologists were blinded to the diagnoses of nocturia and ED. Estimated glomerular filtration rate was calculated using serum creatinine (Cr):  $194 \times \text{serum Cr}^{-1.094} \times \text{age}^{-0.287}$  [Ref. 16]. Diabetic nephropathy was defined as positive when the urine albumin-to-creatinine ratio was  $\geq 300$  mg/g creatinine and/or estimated glomerular filtration rate was <30 mL/min/1.73 m<sup>2</sup> [Ref. 17]. Diabetic neuropathy was diagnosed if the patients showed two or more of the following three characteristics: neuropathic symptoms, the absence of the Achilles reflex or abnormal vibration perception threshold scores assessed with a 128-Hz tuning fork<sup>18</sup>.

### Statistical analysis

Estimations of crude odds ratios (ORs) and their 95% confidence intervals (CIs) were carried out using logistical regression analyses for each of the three outcomes, namely, ED, moderate to severe ED and severe ED, in relation to nocturia. Age, body mass index, hypertension, dyslipidemia, stroke, ischemic heart disease, glycated hemoglobin, current drinking, current smoking, use of insulin, use of oral antihyperglycemic agent and diabetic neuropathy were selected *a priori* as potential confounding factors. Multiple regression logistic analyses were used to adjust for potential confounding factors. All statistical analyses were carried out using SAS software package version 9.4 (SAS Institute, Cary, NC, USA). All probability values for statistical tests were two-tailed, and  $P < 0.05$  was considered statistically significant, using an alpha value of 0.05.

## RESULTS

Among the 332 patients with type 2 diabetes mellitus, the prevalence of nocturia was 79.8%. The prevalence values of nocturia among patients with ED, moderate ED, and severe ED were 95.8%, 57.2% and 42.7%, respectively (Table 1). Table 2 shows crude and adjusted ORs and 95% CIs for the three outcomes regarding ED in relation to nocturia. The prevalence of ED (SHIM <22), moderate to severe ED (SHIM

**Table 1** | Clinical characteristics of the 332 study participants

Variable	n (%)
Mean age (years)	57.1 ± 10.0
Mean BMI (kg/m <sup>2</sup> )	25.2 ± 4.8
Mean HbA1c (%)	7.7 ± 2.0
Mean HbA1c (mmol/mol)	61 ± 22
Mean duration of T2DM (years)	9.6 ± 8.3
Current drinking (%)	198 (59.6)
Current smoking (%)	101 (30.4)
Hypertension (%)	209 (63.0)
Dyslipidemia (%)	243 (73.2)
Diabetic neuropathy (%)	169 (50.9)
Diabetic retinopathy (%)	79 (23.8)
Diabetic nephropathy (%)	31 (9.3)
Stroke (%)	18 (5.4)
Ischemic heart disease (%)	26 (7.8)
Use of insulin (%)	85 (25.6)
Use of oral anti-hyperglycemic agent (%)	216 (65.1)
Mean SHIM score	10.0 ± 6.8
ED, SHIM score <22 (%)	318 (95.8)
Moderate to severe ED, SHIM score <12 (%)	190 (57.2)
Severe ED, SHIM score <8 (%)	142 (42.8)
Nocturia (%)	265 (79.8)

BMI, body mass index; ED, erectile dysfunction; Hb1Ac, glycated hemoglobin; SD, standard deviation; SHIM, Sexual Health Inventory for Men; T2DM, type 2 diabetes mellitus.

**Table 2** | Crude and adjusted odds ratios and 95% confidence intervals for severity of erectile dysfunction

Variable	Prevalence (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Associated with ED (SHIM <22)			
Nocturia			
No	57/67 (85.1)	1.00	1.00
Yes	261/265 (98.5)	11.45 (3.69–42.92)*	7.86 (2.11–33.56)*
Associated with moderate to severe ED (SHIM <12)			
Nocturia			
No	24/67 (35.8)	1.00	1.00
Yes	166/265 (62.6)	3.00 (1.73–5.31)*	2.17 (1.16–4.12)*
Associated with severe ED (SHIM <8)			
Nocturia			
No	18/67 (26.9)	1.00	1.00
Yes	124/265 (46.8)	2.39 (1.35–4.42)*	1.60 (0.83–3.16)

\* $P < 0.01$ . Odds ratios (OR) were adjusted for age, body mass index, hypertension, dyslipidemia, stroke, ischemic heart disease, glycated hemoglobin, current drinking, current smoking, use of insulin, use of oral antihyperglycemic agent and diabetic neuropathy. CI, confidence interval; ED, erectile dysfunction; SHIM, Sexual Health Inventory for Men.

<12), and severe ED (SHIM <8) among patients with nocturia were 98.5% (261/265), 62.6% (166/265) and 46.8% (124/265), respectively. In the crude analysis, nocturia was significantly positively associated with ED, moderate to severe ED and severe ED. After adjustment for age, body mass index,

hypertension, stroke, ischemic heart disease, glycated hemoglobin and diabetic neuropathy, nocturia was independently positively associated with ED and moderate to severe ED: the adjusted ORs were 7.86 (95% CI 2.11–33.56) and 2.17 (95% CI 1.16–4.12), respectively. The positive association between nocturia and severe ED fell just short of significance after adjustment.

## DISCUSSION

The present study is the first to show a significant positive association between nocturia and ED and moderate to severe ED among Japanese patients with type 2 diabetes mellitus. Our findings were in agreement with those of a Taiwanese cross-sectional study of 453 men with type 2 diabetes mellitus, which also showed a positive association between nocturia and ED<sup>14</sup>.

The prevalence of nocturia was higher among participants with diabetes than among those without in a Singapore study of 2,273 individuals<sup>2</sup>, a Taiwanese study of 3,537 women<sup>3</sup>, a Dutch study of 2,934 elderly men<sup>4</sup> and a USA study of 5,506 participants<sup>5</sup>. In a Taiwanese case-control study of 256 women, nocturia scores were higher among women with diabetes than among those without<sup>6</sup>. Diabetes was significantly positively associated with nocturia in a Japanese cross-sectional study of 6,517 participants<sup>19</sup>, two USA cross-sectional studies of 2,484 men<sup>20</sup> and 5,506 adults<sup>7</sup>, respectively, and a Danish study of 2,799 participants<sup>21</sup>.

Among non-diabetic populations, there have been several studies regarding the association between nocturia and ED. In a USA study of 2,301 men aged 30–79 years, nocturia was significantly positively associated with ED<sup>9</sup>. In a Malaysian cross-sectional study of 353 men aged  $\geq 40$  years, nocturia was significantly positively associated with ED<sup>10</sup>. In a Korean study of 365 men with benign prostatic hyperplasia, nocturia was significantly positively associated with ED<sup>11</sup>. In a Japanese cross-sectional study of 2,084 men who underwent multiphasic health screening, nocturia was significantly positively associated with ED after adjustment for age<sup>12</sup>. Similarly, in a Japanese study of 220 consecutive treatment-naive men, nocturia was significantly positively associated with ED<sup>13</sup>.

Among diabetic populations, in contrast, only one previous study has examined the association between nocturia and ED. That study, a Taiwanese cross-sectional study of 453 men with type 2 diabetes mellitus, reported a significant positive association between nocturia (more than two voiding episodes per night) and ED<sup>14</sup>. The prevalence values of nocturia, ED and severe ED in a Taiwanese study were slightly lower than those in the present study: 79.6%, 81.9% and 28.3%, respectively. The present results were partially consistent with those of the Taiwanese study. The discrepancies between the two studies might be explained, at least in part, by differences in race, culture, alcohol habits, smoking status, prevalence of diabetic neuropathy, definition of nocturia and confounding factors considered.

Erectile dysfunction is the most common form of male sexual dysfunction. In a French cross-sectional study of 2,011

men aged 50–80 years, nocturia was significantly positively associated with severe sexual dissatisfaction<sup>22</sup>. In a cross-national study of 1,694 men (including 1,271 men attending urology clinics with lower urinary tract symptoms), nocturia was significantly positively associated with sexual dysfunction<sup>23</sup>.

The mechanism linking nocturia and ED is not well understood. Several mechanisms with varying degrees of overlap between nocturia and ED have been proposed, including alteration of nitric oxide levels, endothelial dysfunction, sex hormones, adrenergic receptors, autonomic hyperactivity, the Rho-kinase pathway and pelvic atherosclerosis<sup>24,25</sup>. Especially among patients with type 2 diabetes, microvascular complications, testosterone level, nitric oxide levels, endothelial dysfunction and subsequent atherosclerosis might be important.

The present study had several limitations. First, because this was a cross-sectional study, we cannot conclude that there is a causal relationship between nocturia and ED. Second, we did not use frequency–volume charts to detect the urine amount. Then, we could not estimate overall urine production, an increase of urine production only at night or reduced nocturnal bladder capacity. Data on nocturia in the present study were self-reported. The questionnaire in the present study might be inadequate to define the prevalence of nocturia<sup>26</sup>. In previous epidemiological studies<sup>2–5,7,9,10,12–14,21</sup>, however, the definition of nocturia was based on self-administered questionnaires. Third, we could not carry out urological examinations. Fourth, data on past and present history of urinary tract infections were not available in the present study. Fifth, the present study sample size was rather small. The lack of a significant association between nocturia and severe ED might be ascribed to insufficient statistical power. Sixth, selection bias could have influenced our results. In two previous Japanese studies of 1,118 men<sup>27</sup> and 197 men with type 2 diabetes mellitus<sup>28</sup>, however, the prevalence values of ED were 90% and 92.9%. The results of the present study were similar to those of the two previous Japanese studies. Finally, we could not control for the participants' partner or socioeconomic status.

In conclusion, nocturia might be positively associated with ED and moderate to severe ED in Japanese patients with type 2 diabetes mellitus. It might be useful if nocturia could serve as an indicator of ED.

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## DISCLOSURE

The authors declare no conflict of interest.

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