


ORIGINAL PAPER

UROLOGY

Mechanisms and grading of nocturia: Results from a multicentre prospective study

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Abstract

Objective: To identify the pathophysiological mechanisms of nocturia and the correlation of these mechanisms with nocturia severity.

Methodology: After approval by the local ethics committee, all patients with nocturia (≥ 1 nocturnal void/night) were included and filled the Overactive Bladder questionnaire, Nocturia Quality of Life, Incontinence Questionnaire - Male Lower Urinary Tract Symptoms (male), International Consultation on Incontinence Questionnaire - Female Lower Urinary Tract Symptoms (female) and 3-day frequency-volume chart. Patients were divided into three groups according to the severity of nocturia: group 1 consisted of patients with mild (1-2 voids/night), group 2 with moderate (3-4 voids/night) and group 3 with severe nocturia (>4 voids/night). Comparative analysis was performed between groups, and $P < .05$ was deemed as statistically significant.

Results: About 68.1%, 64.1% and 8.7% of the patients had nocturnal polyuria (NP), reduced bladder capacity and global polyuria, respectively. 42.7% of the patients had mixed nocturia. 6.1% of the patients did not comply with the aforementioned subtypes and defined as isolated nocturia. Regarding the severity of nocturia, 155 (41%) patients had mild, 167 (45%) patients had moderate and 57 (15%) patients had severe nocturia. Increased nocturia severity was related with decreased quality of life; higher age, urinary tract symptom scores, nocturnal urine volume, evening fluid consumption and beta-blocker medication rates. Increased nocturia severity was also associated with higher NP, global polyuria and reduced bladder capacity rates.

Conclusions: Nocturia mechanisms may vary between mild and moderate to severe nocturia groups according to the present study. Nocturia grading with identification of subtypes may help for better standardisation of the diagnostic and treatment approaches as well as for the design of future clinical trials.

1 | INTRODUCTION

Nocturia is a common condition especially in ageing population and is defined as the complaint of waking at night one or more times to void.¹ The definition has been recently updated as to sleep or intent to sleep after each voiding period which should

be demonstrated by a bladder diary.² There is growing evidence in the last decade that nocturia is not only a part of diseases affecting the lower urinary tract, such as benign prostatic hyperplasia and overactive bladder (OAB), but a distinct entity which may arise from several other medical conditions.³ One of the possible mechanisms mostly included is nocturnal polyuria (NP) defined

as the excessive urine production at night while asleep; >33% of the 24-hour urine production in patients >65 years and >20% of the 24-hour urine production in younger patients.⁴ Global polyuria (24-hour urine volume >40 mL/kg), reduced bladder capacity caused by lower urinary tract dysfunction and primary/secondary sleep disorders constitute the other mechanisms. These different mechanisms need to be explored in all patients presenting with nocturia in order to provide the best treatment approach. However, it is not always possible or easy to obtain a detailed bladder diary in daily clinical practice which is essential for differentiating between aforementioned various pathophysiological mechanisms.

Nocturia has negative impacts on quality of life (QoL) of patients and these impacts are mostly related with the severity of nocturia. Some of the studies concluded that two or more nocturia episodes lead to bother from nocturia and the degree of bother was associated with severity of nocturia.^{5,6} However, there is no consensus on nocturia severity and its impact on QoL of patients, and there are few studies in the existing literature evaluating the mechanisms of nocturia. So, we aimed to identify the pathophysiological mechanisms of nocturia and seek whether proposal of nocturia grading helps for differentiation of the various pathologic conditions.

2 | METHODS

This prospective study was approved by the local ethics committee and patients were included after giving oral and written informed consent. All patients who had nocturia (≥ 1 nocturnal void/night) were included in the study from eight centres between February 2018 and August 2018 with face-to-face interview by an urologist. Patients under the age of 18, with severe neurophysiological disorders (not able to fill questionnaires) and/or with urinary tract infection were excluded from the study.

The demographic characteristics of patients were recorded. All patients filled the Overactive Bladder questionnaire, Nocturia Quality of Life (N-QoL) form and International Consultation on Incontinence Questionnaire - Male Lower Urinary Tract Symptoms (ICIQ-MLUTS) or International Consultation on Incontinence Questionnaire - Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) forms at admission. Also, 3-day frequency-volume chart was filled by patients and the pathophysiological mechanisms of nocturia were determined with this form. Uroflowmetry was performed to all patients. Mechanisms of nocturia were classified into five groups as NP, global polyuria, reduced bladder capacity, mixed nocturia and isolated nocturia.³ We used ICS definition of NP as nocturnal urine volume >33% or >20% of total 24-hour urine volume according to age.⁴ Reduced bladder capacity was described using nocturnal bladder capacity index (NBCi).³ If NBCi is calculated as >0, it states that the bladder itself cannot store the amount of urine produced at night and called as reduced bladder capacity. Global polyuria (24-hour polyuria) was diagnosed when the overall urine volume was >40 mL/kg in adults.³ Mixed polyuria was defined as the combination of NP

What's known

- Nocturia has negative impacts on quality of life of patients and these impacts are mostly related with the severity of nocturia.

What's new

- We believe that nocturia grading with identification of subtypes may help for standardization of the diagnostic and treatment approach as well as for the design of future clinical trials.

and reduced bladder capacity. Nocturia which did not comply with the aforementioned subtypes was defined as isolated nocturia.

Patients were divided into three groups according to the severity of nocturia: group 1 consisted of patients with mild (1-2 voids/night), group 2 consisted of patients with moderate (3-4 voids/night) and group 3 consisted of patients with severe nocturia (>4 voids/night), and these groups were compared in terms of demographic characteristics, voiding symptoms, frequency-volume charts and nocturia subtypes.

2.1 | Statistical analysis

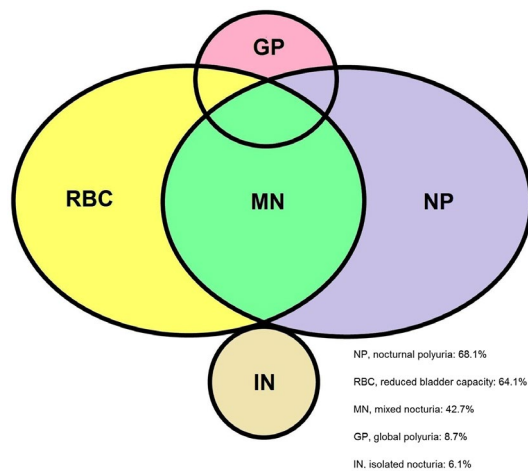
Statistical analyses were performed with the Statistical Package of Social Sciences version 21.0 (SPSS, Chicago, IL). The Kolmogorov-Smirnov and Shapiro-Wilk normality tests were used to determine whether the data were normally distributed or not. As a result of the normality tests, the data were considered to be normally distributed, since the *P* values were greater than .05. Data were presented as means and standard deviation and numbers (*n*) and percent (%). One-way ANOVA test including post hoc analysis and χ^2 test were performed for comparison of variables according to nocturia severity. *P* < .05 was considered statistically significant.

3 | RESULTS

A total of 379 patients from eight centres were included in the study and the mean age of patients was 56.6 ± 12.5 (18-94) years old. Of these patients, 340 (89.7%) were male and 39 (10.3%) were female. The mean body mass index (BMI) was 28.5 ± 5.0 (18.7-49) kg/m² and the most common comorbidity was hypertension (27.2%). The demographic characteristics of patients are given in Table 1. NP was the most common subtype (68.1%); the other subtypes were reduced bladder capacity (64.1%), mixed nocturia (combinations of NP, reduced bladder capacity and global polyuria) (42.7%) and global polyuria (8.7%). However, 6.1% of the patients did not comply with the aforementioned subtypes and this was defined as isolated nocturia, which probably reflects the patients with sleep disorders. The distribution of aetiological factors is given in Figure 1.

TABLE 1 Demographic characteristics of patients included

Age (years) (mean ± SD)	56.6 ± 12.5 (18-94)
Gender (n, %)	
Male	340 (89.7%)
Female	39 (10.3%)
BMI (kg/m ²) (mean ± SD)	28.5 ± 5.0 (18.7-49)
Smoking (n, %)	184 (48.5%)
Alcohol (n, %)	66 (17.4%)
Comorbidity (n, %)	
Hypertension	103 (27.2%)
Diabetes Mellitus	69 (18.2%)
Coronary Artery Disease	45 (11.9%)
Chronic obstructive pulmonary disease	24 (6.3%)
Hyperthyroidism	6 (1.6%)
Hypothyroidism	14 (3.7%)
Congestive heart failure	12 (3.2%)
Diuretic use (n, %)	24 (6.3%)
Beta-blocker use (n, %)	29 (7.7%)

**FIGURE 1** The classification of nocturia mechanisms

Regarding the severity of nocturia, 155 (41%) patients had mild, 167 (45%) patients had moderate and 57 (15%) patients had severe nocturia. Increased nocturia severity was associated with higher age, comorbidities and beta-blocker medication rates ($P = .005$, $P < .001$ and $P = .002$, respectively); however, the BMI values, smoking status and gender were similar between the nocturia severity groups (Table 2). All of the urinary symptom questionnaires' scores used in our study, including ICIQ-FLUTS, ICIQ-MLUTS and OAB, were significantly rising with the increase in nocturia severity (Table 2). Increased nocturia severity was found to be associated with higher daytime urinary frequency, night-time urine volume, total daily urine volume and evening liquid consumption according to 3-day frequency-volume chart results (Table 3). However, there were no significant differences between the nocturia severity groups in terms of maximal flow rates (Q_{max}) in uroflowmetry and postvoiding residual

volumes ($P = .070$ and $P = .267$). Rate of all pathophysiological mechanisms of nocturia was rising with the increase of nocturia severity, especially for mild nocturia compared with moderate-severe nocturia (Table 3).

4 | DISCUSSION

Nocturia is a common health problem worldwide and its prevalence vary between 8.9% and 82.7% according to inclusion criteria, sex and age groups.⁷⁻⁹ In USA, the prevalence of nocturia (≥ 1 voids) was evaluated in different age and sex groups and detected in men as 56.8%, 70.2% and 82.7% in 20-39 years, 40-59 years and ≥ 60 years, respectively; in women as 68.9%, 74.3% and 84.7% in 20-39 years, 40-59 years and ≥ 60 years, respectively.⁸ The nocturia prevalence was noted as 28.4%, 17.6% and 8.9% for nocturia episodes ≥ 1 , ≥ 2 , and ≥ 3 , respectively, in Turkey.⁹ The most common risk factors of nocturia are age, hypertension, higher BMI, metabolic syndrome, diabetes mellitus and cerebrovascular and cardiovascular diseases.^{10,11} Also, nocturia was found to be associated with increased risk of falls, fractures, driving accidents and mortality.¹²⁻¹⁴ Nocturia and nocturia-related morbidities lead serious economic burden on healthcare systems of countries.¹⁵⁻¹⁷ These nocturia-related risks, morbidities and economic burden reveal the importance of timely evaluation and effective nocturia management. The main step of nocturia management is the classification of nocturia according to pathophysiology. Nocturia can be subclassified into four pathophysiological mechanisms: global polyuria (an overall increase of urine production), NP (an increase of urine production only at night), reduced bladder capacity and mixed aetiologies.^{3,18,19} One of the first studies about the classification of nocturia was published by Weiss et al in 1998.²⁰ They classified nocturia into three groups as NP, nocturnal detrusor overactivity (NDO) (including reduced bladder capacity) and mixed (NP+NDO), and retrospectively evaluated the data of 200 consecutive patients with nocturia.²⁰ They detected that 7% of patients had NP, 57% of patients had NDO and 36% of patients had a mixed aetiology.²⁰ They did not add global polyuria in classification, evaluated it separately and they noted that 23% of patients had global polyuria. There were some differences in definitions of nocturia aetiologies in this study; they defined NP as $>33\%$ of the 24-hour urine production and polyuria as >2500 cc urine output in 24 hours. The distribution of nocturia aetiologies was different from our study because of the definition criteria and the unsimilar subclassification of aetiologies. Choi et al evaluated the classification of nocturia in male patients with lower urinary tract symptoms (LUTS).²¹ A total of 521 patients >18 years old were included in the study and 376 (72.2%) patients had NP, 520 (99.8%) patients had reduced bladder capacity, 376 (72.2%) patients have mixed type and 45 (8.6%) patients had global polyuria. Unlike this study, the most common type of nocturia was NP in our study. The patient population may have a significant role in different results of the studies, as they included only male patients with LUTS; however, we evaluated both genders and not only patients with LUTS. Epstein et al compared the nocturia aetiology in black and white male patients who were admitted with LUTS between the years 2008 and 2016.²² They subclassified nocturia as

TABLE 2 Comparison of the groups in terms of patient demographics, urinary symptom scores and quality of life (QoL). It is obvious that scores are rising as the severity of nocturia increases

	Mild nocturia (n = 155)	Moderate nocturia (n = 167)	Severe nocturia (n = 57)	P ¹ mild vs moderate	P ² mild vs severe	P ³ moderate vs severe	P
Age (mean ± SD)	54.0 ± 13.3	58.2 ± 11.7	58.6 ± 12.1	.009	.045	.966	.005
BMI (kg/m ²) (mean ± SD)	28.2 ± 4.8	28.8 ± 5.2	28.4 ± 4.8	.570	.963	.885	.595
Smoking (pack-years) (mean ± SD)	12.2 ± 16.4	12.2 ± 18.7	16.2 ± 18.9	.999	.314	.294	.286
Gender (n, %)							
Male	142	148	50	-	-	-	.587
Female	13	19	7				
Comorbidities (%)	30,8	59,3	66,7	-	-	-	<.001
Diuretic use (%)	6,5	6,6	5,3	-	-	-	.936
Beta-blocker use (%)	1,9	10,8	14	-	-	-	.002
ICIQ-MLUTS voiding score (mean ± SD)	6.5 ± 4.5	8.5 ± 5.1	8.5 ± 4.8	.002	.031	.995	.001
ICIQ-MLUTS storage score (mean ± SD)	3.0 ± 3.2	3.9 ± 3.4	5.1 ± 5.0	.079	.002	.135	.002
ICIQ-FLUTS voiding score (mean ± SD)	7.8 ± 2.9	9.3 ± 3.3	13.0 ± 2.9	.409	.004	.032	.005
ICIQ-FLUTS storage score (mean ± SD)	5.1 ± 3.4	9.2 ± 4.4	10.1 ± 6.9	.055	.073	.895	.033
ICIQ-NqoL				<.001	<.001	<.001	
Q 1-5, 7 (sleep/energy) (mean ± SD)	9.0 ± 6.6	13.7 ± 7.2	17.7 ± 7.2				<.001
ICIQ-NqoL				<.001	<.001	.006	<.00
Q 6, 8-12 (bother/ concern) (mean ± SD)	5.8 ± 4.6	10.3 ± 5.0	12.7 ± 5.5				1
OAB score (mean ± SD)	11.6 ± 6.2	16.5 ± 7.4	20.2 ± 8.3	<.001	<.001	.003	<.001
ICIQ-MLUTS 14a (frequency of nocturia) (mean ± SD)	1.7 ± 0.9	3.0 ± 0.8	3.6 ± 0.6	<.001	<.001	<.001	<.001
ICIQ-MLUTS 14b (QoL) (mean ± SD)	4.8 ± 3.0	6.4 ± 2.9	7.4 ± 2.6	<.001	<.001	.093	<.001
ICIQ-FLUTS 13a (mean ± SD)	0.9 ± 1.8	0.3 ± 0.9	0.8 ± 1.2	.350	.994	.564	.324
ICIQ-FLUTS 13b (mean ± SD)	1.5 ± 3.1	1.3 ± 3.2	4.2 ± 4.4	.990	.222	.151	.156
ICIQ-NqoL				<.001	<.001	.063	<.001
Q 12 (Nocturia based QoL) (mean ± SD)	1.4 ± 1.3	2.9 ± 3.4	3.0 ± 1.2				
ICIQ-NqoL				<.001	<.001	.989	<.001
Q 13 (General QoL) (mean ± SD)	2.0 ± 1.1	2.6 ± 1.0	3.0 ± 1.1				

NP, RBC, mixed (NP+RBC) and other (neither RBC nor NP), and they reported that 24%, 27%, 30% and 19% of white patients had NP, RBC, mixed nocturia and other aetiologies, respectively; while 26%, 30%, 28% and 16% of black patients had NP, RBC, mixed nocturia and other aetiologies, respectively. They noted that the aetiological mechanisms were similar between the groups. The differences between the percentages of nocturia aetiologies from our study may

be also caused by the selection of patient criteria and the differences in the classification of nocturia mechanisms. So, we believe that the standardisation of classification of nocturia mechanisms is important to speak the same language.

Nocturia has negative impacts on QoL of patients and leads to decrease in productivity at work.^{5,15,16,23,24} The effects of nocturia on QoL are mostly related with the severity of nocturia. Although

TABLE 3 Comparison of the severity groups according to 3-day frequency-volume chart and nocturia mechanisms

	Mild nocturia (n = 155)	Moderate nocturia (n = 167)	Severe nocturia (n = 57)	P ¹ mild vs moderate	P ² mild vs severe	P ³ moderate vs severe	P
Daytime urinary frequency (mean ± SD)	5.7 ± 2.2	6.5 ± 2.4	8.0 ± 4.4	.045	<.001	.002	<.001
Frequency of nocturia (mean ± SD)	1.5 ± 0.4	3.3 ± 0.4	6.1 ± 2.3	<.001	<.001	<.001	<.001
Daytime urine volume (mL) (mean ± SD)	1534.2 ± 479.6	1461.7 ± 563.9	1440.7 ± 708.9	.473	.524	.967	.397
Night-time urine volume (mL) (mean ± SD)	458.7 ± 257.5	710.7 ± 302.2	898.1 ± 538.9	<.001	<.001	<.001	<.001
Total daily urine volume (mL) (mean ± SD)	1992.9 ± 578.9	2172.5 ± 719.3	2343.0 ± 1069.1	.072	.006	.283	.005
Daytime max urine volume (mL) (mean ± SD)	361.9 ± 143.3	288.4 ± 100.0	236.8 ± 114.6	<.001	<.001	.016	<.001
Daytime liquid consumption (mL) (mean ± SD)	2031.6 ± 652.7	1939.1 ± 889.7	2177.1 ± 1164.7	.594	.513	.164	.180
Evening liquid consumption (mL) (mean ± SD)	792.7 ± 366.9	849.5 ± 659.7	1060.8 ± 707.3	.642	.007	.041	.010
Total liquid consumption (mL) (mean ± SD)	2824.3 ± 887.4	2788.6 ± 1417.0	3238.0 ± 1702.7	.966	.094	.059	.063
Qmax (mL/sn) (mean ± SD)	17.2 ± 7.8	16.3 ± 8.4	14.4 ± 7.3	.557	.056	.255	.070
PVR (mL) (mean ± SD)	66.6 ± 65.7	58.2 ± 60.5	73.1 ± 78.5	.485	.797	.301	.267
Nocturnal polyuria (%)	45,2	84,4	82,5	-	-	-	<.001
Global polyuria (%)	3,9	10,8	15,8	-	-	-	.011
Reduced bladder capacity (%)	50,3	70,7	82,5	-	-	-	<.001
Mixed nocturia (%)	18,1	57,5	66,7	-	-	-	<.001
Isolated nocturia (%)	9,4	0	0	-	-	-	<.001

one or more times wake up to void at night is defined as nocturia, it was noted that most of the patients with one nocturia episode had no bother or some of the older patients considered this as a normal consequence of ageing.^{5,23,24} Tikkinen et al evaluated the association between the nocturia severity and the health-related QoL (HRQoL) of individuals using the generic 15 dimension instrument.⁵ Bother of nocturia was evaluated with four-point scale (none, small, moderate and major) and they noted that majority of patients with one nocturia episode had no significant bother, however, patients with two episodes of nocturia had small bother and patients with three or more nocturia episodes had moderate or major bother. Also, they reported that ≥2 voids per night were associated with impaired HRQoL. We classified the nocturia severity as mild, moderate and severe in our study and reached similar results as they did. Additionally, we used a nocturia-specific quality of life questionnaire, N-QoL, which was firstly described by Abraham et al²⁵ and we found that increased severity of nocturia was associated with impaired QoL of patients in concordance with previous studies.^{5,25} Zhang et al evaluated the prevalence and risk factors of nocturia and nocturia-related QoL in Chinese population with 1198 adults.²⁶ They also used the N-QoL

questionnaire and they reported that increasing episodes of nocturia and decreasing total sleeping hours were independent factors predicting a significantly lower N-QoL score. Also, they noted that two or more nocturia episodes were associated with worse N-QoL scores as we did. Fitzgerald et al evaluated the data of 5506 adults at ages 30 to 79 from Boston Area Community Health (BACH) study; they detected the nocturia prevalence as 28.4% and the individuals with nocturia had lower self-rated mental and physical health scores.¹³ However, they did not specify the association with nocturia severity and these scores. Choi et al assessed the mediating role of sleep quality in the association between the nocturia and HRQoL with 500 patients above 40 years old.²⁷ They reported that ≥2 nocturia episodes were associated with decreased HRQoL and this association was mediated by sleep quality. Although some of the studies presented the threshold ≥2 nocturia episodes for nocturia severity, there has been no consensus about the severity of nocturia and treatment requirements of patients regarding nocturia severity in the existing literature yet. So, we propose a grading standardisation for nocturia severity as mild (1-2 voids/night), moderate (3-4 voids/night) and severe nocturia (>4 voids/night) and demonstrate that

increase in nocturia severity was associated with decreased QoL as well as different rates of pathophysiological mechanisms.

We also faced that all scores for standardised LUTS questionnaires used in the present study were higher in more severe nocturia groups. Abdelmoteleb et al evaluated the association between the ICIQ-bladder diary and the ICIQ-LUTS.²⁸ They noted that the agreement level between the ICIQ-bladder diary and the ICIQ-LUTS for nocturia symptoms was better than that of daytime frequency in both genders and the agreement level was also higher in the extreme of frequencies. Both voiding and storage scores of ICIQ-MLUTS and ICIQ-FLUTS were also correlated with nocturia severity in our study. Given the fact that the severity of nocturia was diagnosed with a bladder diary in the present study, our findings support previous studies for the concordance of voiding questionnaires and bladder diary.

Several studies reported that the prevalence and severity of nocturia were increased with ageing.^{9,29} Vaughan et al detected that half of the patients with older age had ≥ 2 nocturia episodes; however, this rate was only 15%-20% in younger patients. Also, they noted that the number of comorbidities was higher in patients with more nocturia frequency. Patients with moderate and severe nocturia were older and had more comorbidities need to be treated than mild nocturia in our study.

Although the treatment of baseline pathology is essential in patients with nocturia, precautions in lifestyle changes, such as restriction in evening fluid intake, may be enough in mild nocturia. Pharmacological therapies are recommended after the failure of lifestyle changes and behavioural treatments.³⁰ So, the increase in nocturia severity negatively effects the patients' QoL and increased urinary symptom scores may cause the failure of lifestyle changes and behavioural treatments and may require additional treatments to lifestyle changes in patients with moderate and severe nocturia. As all physicians cannot evaluate patients with frequency-volume chart because of excessive daily workload in some regions, grading of nocturia may help for management of patients in daily clinical practice.

4.1 | Limitations

This study is not without limitations. Number of participants from eight centres seem less compared with previous studies. We believe that face-to-face design may overcome this limitation as more standardised data are driven for the study. We also did not evaluate for sleep disorders specifically, as we aimed at looking for urological disorders. However, isolated nocturia group in the present study may reflect the sleep disorders as mentioned previously.

4.2 | Conclusions

Nocturia has negative impacts on QoL of patients and the impact rises with the increase of nocturia severity. Nocturia-related

pathophysiological factors may vary between mild, moderate and severe nocturia groups. We believe that nocturia grading with identification of subtypes may help for standardisation of the diagnostic and treatment approach as well as for the design of future clinical trials.

DISCLOSURES

None.

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