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

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Abstract

Objective: To identify 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 (OABq), nocturia quality of life (N-QoL), ICIQ-MLUTS (male), ICIQ-FLUTS (female) and 3-day frequency-volume chart. Patients were divided into three groups according 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 were performed between groups, p<0.05 was deemed as statistically significant. Results: 68.1%, 64.1% and 8.7% of the patients had nocturnal polyuria, 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 afore-mentioned 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 nocturnal polyuria, 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 standardization of the diagnostic and treatment approaches as well as for the design of future clinical trials.

Introduction

Nocturia is a common condition especially in aging 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 (BPH) 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 due to 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 afore-mentioned 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 pathophysiological mechanisms of nocturia and seek whether proposal of nocturia grading helps for differentiation of the various pathologic conditions.

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 centers between February 2018 and August 2018 with face-to-face interview by a urologist. Patients under the age 18, with severe neurophysicological disorders (not able to fill questionnaires) and/or with urinary tract infection were excluded from study.

The demographic characteristics of patients were recorded. All patients filled the overactive bladder questionnaire (OABq), 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 in five groups as nocturnal polyuria, global polyuria, reduced bladder capacity, mixed nocturia and isolated nocturia.[3] We used ICS definition of nocturnal polyuria as nocturnal urine volume >33% or >20% of total 24-hour urine volume according to age.[4] Reduced bladder capacity was described with 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-h polyuria) was diagnosed when the overall urine volume >40ml/kg in adults.[3] Mixed polyuria was defined as the combination of nocturnal polyuria and reduced bladder capacity. Nocturia which did not comply with the afore-mentioned 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.

Statistical analysis

Statistical analyses were performed with the Statistical Package of Social Sciences version 21.0 (SPSS, Chicago, IL). The SPSS normality test was used to determine whether the data were normally distributed or not. Because the skewness and kurtosis values of our data were distributed within ±1.5 range10 it was decided that the data were distributed normally. Data were presented as means and standard deviation and numbers (n) and percent (%). One-Way ANOVA test including post-hoc analysis and $\chi 2$ test were performed for comparison of variables according to nocturia severity. P<0.05 was considered statistically significant.

Results

A total of 379 patients from eight centers were included in 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 BMI was 28.5±5.0 (18.7-49) kg/m^2 and the most common co-morbidity was hypertension (27.2%). The demographic characteristics of patients were given in Table 1. Nocturnal polyuria was the most common subtype (68.1%); the other subtypes were reduced bladder capacity (64.1%), mixed nocturia (combinations of nocturnal polyuria, reduced bladder capacity and global polyuria) (42.7%) and global polyuria (8.7%). However, 6.1% of the patients did not comply with the afore-mentioned subtypes and this was defined as isolated nocturia which probably reflects the patients with sleep disorders. The distribution of etiological factors is given in

Figure 1.

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=0.005, p<0.001 and p=0.002 respectively); however the body mass index (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 (Qmax) in uroflowmetry and post-voiding residual volumes (p=0.070 and p= 0.267). Rate of all pathophysiological mechanisms of nocturia were rising with the increase of nocturia severity, especially for mild nocturia compared to moderate-severe nocturia (Table 3).

Discussion:

Nocturia is a common health problem in world-wide and its prevalence vary between 8.9%-82.7% according to inclusion criteria, sex and age groups.[7-9] In US 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, or [?] 3 respectively, in Turkey.[9] The most common risk factors of nocturia are age, hypertension, higher body mass index (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 health care 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 sub-classified into four pathophysiological mechanisms: global polyuria (an overall increase of urine production), nocturnal polyuria (an increase of urine production only at night), reduced bladder capacity and mixed of etiologies.[3,18,19] One of the first studies about the classification of nocturia was published by Weiss et al at 1998.[20] They classified the nocturia in three groups as nocturnal polyuria (NP), nocturnal detrusor overactivity (NDO) (including reduced bladder capacity) and mixed (NP+NDO) and retrospectively evaluated the data of 200 consecutive patientswith nocturia.[20] They detected that 7% of patients had nocturnal polyuria, 57% of patients had NDO and 36% of patients had a mixed etiology.[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 etiologies in this study; they defined nocturnal polyuria as > 33% of the 24-hour urine production and polyuria as >2500 cc urine output in 24 hours. The distribution of nocturia etiologies was different from our study because of definition criteria and the unsimilar subclassification of etiologies. 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 nocturnal polyuria, 520 (99.8%) patients had reduced bladder capacity, 376 (72.2%) patients has mixed type and 45 (8.6%) patients had global polyuria. Unlike this study the most common type of nocturia was nocturnal polyuria 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 etiology in black and white male patients who admitted with LUTS between the years 2008 and 2016.[22]They subclassified nocturia as 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 etiologies respectively; while 26%, 30%, 28% and 16% of black patients had NP, RBC, mixed nocturia and other etiologies respectively. They noted that the etiological mechanisms were similar between the groups. The differences between the percentages of nocturia etiologies form our study may be also due to the selection of patient criteria and the differences in the classification of nocturia

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mechanisms. So we believe that the standardization of classification of nocturia mechanisms is important to speak the same language.

Nocturia has negative impacts on quality of life (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 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 aging.[5,23,24] Tikkinen et al. evaluated the association between the nocturia severity and the health related QoL (HRQoL) of individuals with using generic 15 dimension instrument.[5] Bother of nocturia was evaluated with four-point scale (none, small, moderate, 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 al[25]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 quality of life in Chinese population with 1198 adults.[26] They used also 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 to nocturia severity in the existing literature yet. So, we propose a grading standardization 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 quality of life as well as different rates of pathophysiological mechanisms.

We also faced that all scores for standardized 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 at 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 was increased with aging.[9,29] Vaughan et al detected that the 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 co-morbidities were higher in patients with more nocturia frequency. Patients with moderate and severe nocturia were older and had more comorbidities need to treat than mild nocturia in our study.

Although the treatment of baseline pathology is essential in patients with nocturia, precautions in lifestyle changes like restriction in evening fluid intake may be enough in mild nocturia. Pharmacological therapies are recommended after the failure of lifestyle changes and behavioral treatments.[30] So the increase in nocturia severity negatively effects the patients' quality of life and increased urinary symptom scores may cause the failure of lifestyle changes and behavioral 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 due to excessive daily work-load in some regions; grading of nocturia may help for management of patients in daily clinical practice.

Limitations: This study is not without limitations. Number of participants from eight centers seem less compared to previous studies. We believe that face-to-face design may overcome this limitation as more standardized data 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.

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 standardization of the diagnostic and treatment approach as well as for the design of future clinical trials.

Conflict of interest: none declared

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References:

1. van Kerrebroeck P, Abrams P, Chaikin D, et al. The standardisation of terminology in nocturia: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21:179-83.*https://doi.org/*10.1002/nau.10053

2. Hashim H, Blanker MH, Drake MJ et al. International Continence Society (ICS) report on the terminology for nocturia and nocturnal lower urinary tract function. Neurourol Urodyn 2019;38:499–508.*https://doi.org/*10.1002/nau.23917.

3. Cornu JN, Abrams P, Chapple CR, et al. A contemporary assessment of nocturia: definition, epidemiology, pathophysiology, and management–a systematic review and meta-analysis. Eur Urol 2012;62:877-90.*https://doi.org/*10.1016/j.eururo.2012.07.004.

4. Weiss JP, Wein AJ, van Kerrebroeck P, et al. Nocturia: new directions. Neurourol Urodyn 2011;30:700–3.*https://doi.org/*10.1002/nau.21125.

5. Tikkinen KAO, Johnson TM, Tammela RLJ, et al. Nocturia frequency, bother and quality of life: How often is too often? A population-based study in Finland. Eur Urol 2010;57:488–96.*https://doi.org/*10.1016/j.eururo.2009.03.080.

6. Yu HJ, Chen FY, Huang PC, Chen TH, Chie WC, Liu CY. Impact of nocturia on symptom-specific quality of life among community-dwelling adults aged 40 years and older. Urology 2006;67:713-8.*https://doi.org/*10.1016/j.urology.2005.10.054 .

7. Chow PM, Liu SP, Chuang YC, et al. The prevalence and risk factors of nocturia in China, South Korea, and Taiwan: results from a cross-sectional, population-based study. World J Urol 2018;36:1853-1862.*https://doi.org/*10.1007/s00345-018-2329-0.

8. Soysal P, Cao C, Xu T, et al. Trends and prevalence of nocturia among US adults, 2005-2016. Int Urol Nephrol. 2020;52:805-813. https://doi.org/10.1007/s11255-019-02361-5.

9. Zumrutbas AE, Bozkurt AI, Alkis O, Toktas C, Cetinel B, Aybek Z. The Prevalence of Nocturia and Nocturnal Polyuria: Can New Cutoff Values Be Suggested According to Age and Sex? Int Neurourol J 2016;20:304-310.*https://doi.org/*10.5213/inj.1632558.279.

10. Tikkinen KA, Auvinen A, Johnson TM 2nd, et al. A systematic evaluation of factors associated with nocturia—the population-based FINNO study. Am J Epidemiol 2009;170:361-8.*https://doi.org/*10.1093/aje/kwp133.

11. Kim SY, Bang W, Kim MS, Park B, Kim JH, Choi HG. Analysis of the Prevalence and Factors Associated with Nocturia in Adult Korean Men. Sci Rep 2017;7:41714.*https://doi.org/*10.1038/srep41714.

12. Kupelian V, Fitzgerald MP, Kaplan SA, Norgaard JP, Chiu GR, Rosen RC. Association of nocturia and mortality: results from the Third National Health and Nutrition Examination Survey. J Urol 2011;185:571-7.*https://doi.org/*10.1016/j.juro.2010.09.108.

13. Fitzgerald MP, Litman HJ, Link CL, McKinlay JB; BACH Survey Investigators.The association of nocturia with cardiac disease, diabetes, body mass index, age and diuretic use: results from the BACH survey. J Urol 2007;177:1385-9.*https://doi.org/10.1016/j.juro.2006.11.057* .

14. Pesonen JS, Cartwright R, Vernooij RWM, et al.; CLUE Working Group. The Impact of Nocturia on Mortality: A Systematic Review and Meta-Analysis. J Urol. 2020;203:486-495.*https://doi.org/*10.1097/JU.0000000000000463.

15. Dmochowski R, Brucker BM, Cole E, et al. Economic burden of illness in adult patients with nocturia. J Manag Care Spec Pharm 2019;25:593-604.*https://doi.org/*10.18553/jmcp.2019.18067.

16. Jhaveri J, Gauthier-Loiselle M, Gagnon-Sanschagrin P, Wu EQ. The Economic Burden of Nocturia on the U.S. Health Care System and Society: A National Health and Nutrition Examination Survey Analysis. J Manag Care Spec Pharm 2019;25:1398-1408.*https://doi.org/*10.18553/jmcp.2019.19191.

17. Weidlich D, Andersson FL, Oelke M, Drake MJ, Jonasson AF, Guest JF. Annual direct and indirect costs attributable to nocturia in Germany, Sweden, and the UK. Eur J Health Econ 2017;18:761-771.*https://doi.org/*10.1007/s10198-016-0826-x.

18. Sakalis VI, Karavitakis M, Bedretdinova D, et al. Medical Treatment of Nocturia in Men with Lower Urinary Tract Symptoms: Systematic Review by the European Association of Urology Guidelines Panel for Male Lower Urinary Tract Symptoms. Eur Urol 2017;72:757-769.*https://doi.org/*10.1016/j.eururo.2017.06.010.

19. Fine ND, Weiss JP, Wein AJ. Nocturia: consequences, classification, and management. F1000Res 2017;6:1627.*https://doi.org/*10.12688/f1000research.11979.1.

20. Weiss JP, Blaivas JG, Stember DS, Brooks MM. Nocturia in adults: etiology and classification. Neurourol Urodyn 1998;17:467-72.*https://doi.org/10.1002/(sici)1520-6777(1998)17:5<467::aid-nau2>3.0.co;2-b* .

21. Choi YS, Kim JC, Kim YH, Choi JB, Park WH, Lee DH. Classification of nocturia by analyzing frequency volume chart and relations with international prostate symptom score in male patients with lower urinary tract symptoms in Korea. Investig Clin Urol 2019;60:267-274.*https://doi.org/*10.4111/icu.2019.60.4.267.

22. , , , et al. Comparison of nocturia etiology in black and white male patients. Can J Urol 2019;26:9769-9773.

23. Kobelt G, Borgstrom F, Mattiasson A. Productivity, vitality and utility in a group of healthy professionally active individuals with nocturia. BJU Int 2003;91:190-95.*https://doi.org/10.1046/j.1464-410x.2003.04062.x* .

24. Bing MH, Moller LA, Jennum P, Mortensen S, Lose G. Validity and reliability of a questionnaire for evaluating nocturia, nocturnal enuresis and sleep-interruptions in an elderly population. Eur Urol 2006;49:710–9.*https://doi.org/10.1016/j.eururo.2005.11.034* .

25. Abraham L, Hareendran A, Mills IW, et al. Development and validation of a quality-of-life measure for men with nocturia. Urology 2004;63:481-6.*https://doi.org/10.1016/j.urology.2003.10.019* .

26. Yamanishi T, Fuse M, Yamaguchi C, et al. Nocturia Quality-of-Life questionnaire is a useful tool to predict nocturia and a risk of falling in Japanese outpatients: a cross-sectional survey. Int J Urol 2014;21:289-93.*https://doi.org/*10.1111/iju.12242.

27. Choi EPH, Wan EYF, Kwok JYY, Chin WY, Lam CLK. The mediating role of sleep quality in the association between nocturia and health-related quality of life. Health Qual Life Outcomes 2019;17:181.*https://doi.org/10.1186/s12955-019-1251-5*.

28. Abdelmoteleb H, Kamel MI, Hashim H. The association between the ICIQ-LUTS and the ICIQ-bladder diary in assessing LUTS. Neurourol Urodyn 2017;36:1601-1606.*https://doi.org/*10.1002/nau.23162.

29. Vaughan CP, Fung CH, Huang AJ, Johnson TM Nd, Markland AD. Differences in the Association of Nocturia and Functional Outcomes of Sleep by Age and Gender: A Cross-sectional, Population-based Study. Clin Ther 2016;38:2386-2393.*https://doi.org/*10.1016/j.clinthera.2016.09.009.

30. Oelke M, De Wachter S, Drake MJ, et al. A practical approach to the management of nocturia. Int J Clin Pract 2017;71:e13027.*https://doi.org/*10.1111/ijcp.13027.

Figure legends:

Figure 1. The classification of nocturia mechanisms.

Table 1. Demographic characteristics of patients included.

Age (years) (mean±SD)
Gender (n, %) Male Female
BMI (kg/m^2) (mean±SD)
Smoking (n, %)
Alcohol (n, %)
Co-morbidity (n, %) Hypertension Diabetes Mellitus Coronary Artery Disease Chronic obstructive pulmona
Diuretic use (n, %)
Beta blocker use (n, %)

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	0.009	0.045	0.966	**0.005**
BMI (kg/m^2) (mean±SD)	28.2±4.8	28.8±5.2	28.4±4.8	0.570	0.963	0.885	0.595
Smoking (pack-years) (mean±SD)	12.2±16.4	12.2±18.7	16.2±18.9	0.999	0.314	0.294	0.286
Gender (n,%) Male Female	142 13	148 19	50 7	-	-	-	0.587
Comorbidities (%)	30,8	59,3	66,7	-	-	-	**<0.001**
Diuretic use (%)	6,5	6,6	5,3	-	-	-	0.936
Beta-blocker use (%)	1,9	10,8	14	-	-	-	**0.002**
ICIQ-MLUTS voiding score (mean±SD)	6.5±4.5	8.5±5.1	8.5±4.8	0.002	0.031	0.995	**0.001**
ICIQ-MLUTS storage score (mean±SD)	3.0±3.2	3.9±3.4	5.1±5.0	0.079	0.002	0.135	**0.002**

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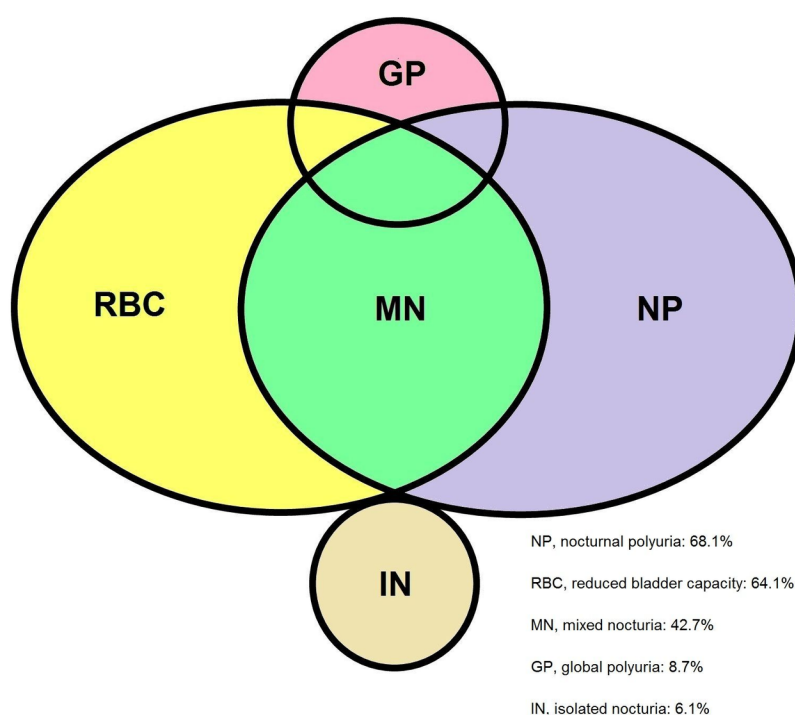|	Mild nocturia (n=155)	Moderate nocturia (n=167)	Severe nocturia (n=57)	P¹ Mild vs Moderate	P² Mild vs Severe	P³ Moderate vs Severe	P
ICIQ-FLUTS voiding score (mean±SD)	7.8±2.9	9.3±3.3	13.0±2.9	0.409	0.004	0.032	**0.005**
ICIQ-FLUTS storage score (mean±SD)	5.1±3.4	9.2±4.4	10.1±6.9	0.055	0.073	0.895	**0.033**
ICIQ-NqoL Q 1-5, 7 (sleep/energy) (mean±SD)	9.0±6.6	13.7±7.2	17.7±7.2	<0.001	<0.001	<0.001	**<0.001**
ICIQ-NqoL Q 6, 8-12 (bother/concern) (mean±SD)	5.8±4.6	10.3±5.0	12.7±5.5	<0.001	<0.001	0.006	**<0.001**
OAB score (mean±SD)	11.6±6.2	16.5±7.4	20.2±8.3	<0.001	<0.001	0.003	**<0.001**
ICIQ-MLUTS 14a (frequency of nocturia) (mean±SD)	1.7±0.9	3.0±0.8	3.6±0.6	<0.001	<0.001	<0.001	**<0.001**
ICIQ-MLUTS 14b (QoL) (mean±SD)	4.8±3.0	6.4±2.9	7.4±2.6	<0.001	<0.001	0.093	**<0.001**
ICIQ-FLUTS 13a (mean±SD)	0.9±1.8	0.3±0.9	0.8±1.2	0.350	0.994	0.564	**0.324**
ICIQ-FLUTS 13b (mean±SD)	1.5±3.1	1.3±3.2	4.2±4.4	0.990	0.222	0.151	0.156

	Mild nocturia (n=155)	Moderate nocturia (n=167)	Severe nocturia (n=57)	P¹ Mild vs Moderate	P² Mild vs Severe	P³ Moderate vs Severe	P
ICIQ-NqoL Q 12 (Nocturia based QoL) (mean±SD)	1.4±1.3	2.9±3.4	3.0±1.2	<0.001	<0.001	0.063	**<0.001**
ICIQ-NqoL Q 13 (General QoL) (mean±SD)	2.0±1.1	2.6±1.0	3.0±1.1	<0.001	<0.001	0.989	**<0.001**

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)	P¹ Mild vs Moderate	P² Mild vs Severe	P³ Moderate vs Severe	P
Daytime urinary frequency (mean±SD)	5.7±2.2	6.5±2.4	8.0±4.4	**0.045**	**<0.001**	**0.002**	**<0.001**
Frequency of nocturia (mean±SD)	1.5±0.4	3.3±0.4	6.1±2.3	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Daytime urine volume (ml) (mean±SD)	1534.2±479.6	1461.7±563.9	1440.7±708.9	0.473	0.524	0.967	0.397
Night-time urine volume (ml) (mean±SD)	458.7±257.5	710.7±302.2	898.1±538.9	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Total daily urine volume (ml) (mean±SD)	1992.9±578.9	2172.5±719.3	2343.0±1069.1	**0.072**	**0.006**	**0.283**	**0.005**

	Mild nocturia (n=155)	Moderate nocturia (n=167)	Severe nocturia (n=57)	P¹ Mild vs Moderate	P² Mild vs Severe	P³ Moderate vs Severe	P
Daytime max urine volume (ml) (mean±SD)	361.9±143.3	288.4±100.0	236.8±114.6	**<0.001**	**<0.001**	**0.016**	**<0.001**
Daytime liquid consumption (ml) (mean±SD)	2031.6±652.7	1939.1±889.7	2177.1±1164.7	0.594	0.513	0.164	0.180
Evening liquid consumption (ml) (mean±SD)	792.7±366.9	849.5±659.7	1060.8±707.3	**0.642**	**0.007**	**0.041**	**0.010**
Total liquid consumption (ml) (mean±SD)	2824.3±887.4	2788.6±1417.0	3238.0±1702.7	0.966	0.094	0.059	0.063
Qmax (ml/sn) (mean±SD)	17.2±7.8	16.3±8.4	14.4±7.3	0.557	0.056	0.255	0.070
PVR (ml) (mean±SD)	66.6±65.7	58.2±60.5	73.1±78.5	0.485	0.797	0.301	0.267
Nocturnal polyuria (%)	45,2	84,4	82,5	-	-	-	**<0.001**
Global polyuria (%)	3,9	10,8	15,8	-	-	-	**0.011**
Reduced bladder capacity (%)	50,3	70,7	82,5	-	-	-	**<0.001**
Mixed nocturia (%)	18,1	57,5	66,7	-	-	-	**<0.001**
Isolated nocturia (%)	9.4	0	0	-	-	-	**<0.001**

GP

RBC   MN   NP

IN

NP, nocturnal polyuria: 68.1%

RBC, reduced bladder capacity: 64.1%

MN, mixed nocturia: 42.7%

GP, global polyuria: 8.7%

IN. isolated nocturia: 6.1%

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