**EFFECT OF DIURESIS ON BOTHER
RELATED TO LOWER URINARY TRACT SYMPTOMS.**

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Abstract

Aims: To explore and objectify the impact of diuresis on the presence of daytime and nighttime LUTS, and associated bother.

Methods: Participants (healthy volunteers and patients referred to our hospital for a urologic consultation) were asked to complete a 72h-bladder-diary and also had to fill in a Likert scale (0: no bother; 10: maximal bother) to evaluate the LUTS-associated bother during daytime and nighttime. Three groups were defined: no/mild bother ($\text{Bother} \leq 2$), moderate bother ($3 \leq \text{Bother} \leq 6$) and strong bother ($\text{Bother} \geq 7$).

Questionnaires in order to assess LUTS (ICIQ MLUTS and ICIQ FLUTS), quality of life (SF-36, N-QoL) and quality of sleep (PSQI) were completed.

Results: Participants with strong bother associated with LUTS documented a statistically significant higher fluid intake during both day and night than individuals who were not bothered (1640mL vs. 1800mL during daytime, $p=0.007$)

Higher diuresis rate induced more LUTS -related bother than was reported in lower diuresis groups (71.3 mL/h in group 1 vs 87.3mL/h in group 3 ($p<0,001$) during daytime).

As might be expected, the lower urinary tract does play a role. An example is the urinary bladder, where the lower the maximal voided volume, the more bother the participants described.

Conclusion: Diuresis rate is implicated in the genesis of bother in patients with LUTS.

KEYWORDS: Lower urinary tract symptoms, diuresis, quality of life.

What's already known about this topic?

When considering Lower Urinary Tract Symptoms, only bladder and prostate are considered. Kidneys and diuresis are always kept apart.

It is already known that reducing fluid intake can improve symptoms in women with urine incontinence.

What does this article add?

Nevertheless, even if it seems logical, the association between urine production and LUTS has never been demonstrated.

This article shows such an association and constitutes a strong proof that conservative management with decrease of fluid intake is a first step of treatment of patients with LUTS.

This constitutes a useful information for general practitioners, urologists and other specialists in clinical practice.

INTRODUCTION

Lower urinary tract symptoms (LUTS), be they storage symptoms (increased daytime frequency, nocturia, urgency, urinary incontinence), or voiding (slow stream, hesitancy...) are known negatively impact quality of life for both women and men across the lifespan[1]. These bothersome issues bring patients to consult with their general practitioner or urologist for evaluation, explanation and cure.

The normal process of micturition implies the succession of filling and emptying phases and involves the bladder, as a storage organ and the bladder outlet (external and internal urethral sphincter, prostate in men) as a continence system. This complex mechanism is neurologically controlled by multiple areas of the nervous system (peripheral, central nervous system, cortical and spinal)[2].

Aside from dysfunction of the neural drive mechanisms, it is commonly accepted that LUTS are related to disorders of the bladder, prostate or urethra due to the fact that they are anatomically or functionally directly involved in the normal bladder cycles.

However, urine production at the level of the kidneys may also play a role and should therefore not be ignored when evaluating LUTS. Diuresis rate may modify the bother of a patient with lower urinary tract dysfunction, enhancing or reducing urinary symptoms depending upon the sensorial stimulation caused by the amount of urine produced. Bladder fullness is related to stretch receptors in the detrusor muscle inducing greater afferent activity as the bladder fills towards capacity. Reduced bladder sensation can be considered as a diminished sensation throughout filling; increased bladder sensation refers to first urge to void at a low bladder volume[3]. A reduced bladder sensation can coexist with other pathology and markedly reduce warning time. Older people, in particular are thus more vulnerable to incontinence.

The dual aim of this study was:

- to objectify the impact of diuresis on the presence and associated bother of day and night LUTS.
- to evaluate the bother related to LUTS in different groups of patients during daytime or nighttime.

MATERIALS AND METHODS

Study design

Patients of any age who were referred to the outpatient clinic of our tertiary referral hospital for a urologic consultation were eligible for inclusion in the study. Eligible patients were presenting with no- LUTS disorders, e.g. vasectomy, infertility, testicle pain, follow-up for asymptomatic kidney stones, although some participants described storage, voiding or post-micturition symptoms, as defined by the International Continence Society [3].

In order to reach patients without any urologic issue, healthy volunteers were recruited from the researchers' surrounding. No compensation, reward, or incentive was offered in exchange for participation in the study.

Patients were excluded from the study if they were younger than 16 years old or if they declined research informed consent.

Participants were informed of the study during routine consultations and were recruited after informed consent was obtained.

Study tasks included completion of a 72h-bladder-diary recording the volume and timing of every void and drink during three 24h-periods (from first morning void on day 1 to the first morning void of day 2). Each 24h-period of the 72h-bladder diary was evaluated separately. Micturition, frequency and volumes, time of waking up, and going to bed in the evening and fluid intake were referenced by patients and extracted for analysis.

The nocturia index was calculated by dividing the nocturnal urine production by the maximum voided volume.

The diurnal bladder capacity index was calculated by dividing the diurnal urine production by the maximal voided volume.

An overview of all the parameters analyzed in this study is provided in appendix.

In order to evaluate the LUTS-associated bother at the end of the day and when waking up in the morning, participants allocated a score to denote the bother associated with each daytime and nighttime period (Likert scale where 0 denoted no bother through to 10 which indicated maximal bother).

Patients also asked self-completed questionnaires that assessed LUTS severity, quality of life, and sleep parameters.

The male and the female versions of the ICI questionnaire (ICIQ MLUTS and ICIQ FLUTS) (three items: filling, voiding, and incontinence symptoms) (overall score ranges from 0 to 47), completed by the ICIQ-OAB allowed us to evaluate storage (0-16 overall score with greater values indicating increased symptom severity), emptying and incontinence symptoms for each participant.

Quality of life was evaluated using the SF36 questionnaire (0-100 score, the lower the score the more disability) and the N-QoL developed by the International Consultation on Incontinence group. N-QoL (0-52 overall score with greater values indicating increased impact on quality of life) assessed the quality of life of patients with nocturia.

Quality of sleep was also evaluated utilizing the modified Pittsburgh sleep quality index (PSQI, overall score ranging from 0 to 21, where lower scores denote a healthier sleep quality). After completion of the questionnaires and bladder diary measurements there were no further study tasks and participants continued to receive usual clinical care.

An overview of the definitions and derivations used in this study is provided in appendix.

The study was approved by the local research ethics committee (EC2016/0433).

Statistical analysis

The data were entered into SPSS statistics version 24 for Windows (IBM Corp, Armonk, NY, USA). After calculating the "mean bother" during daytime and nighttime for each participant, three groups were defined: no/mild bother ($\text{Bother} \leq 2$ on Likert score) (group 1), moderate bother ($3 \leq \text{Bother} \leq 6$) (group 2) and strong bother

(Bother $\geq$ 7) (group 3). Each 24h-period was subdivided into a daytime (after waking up) and nighttime (after going to sleep) period (the first morning void was included in nocturnal urine volume, but not in nighttime frequency).

Categorical and continuous variables were analyzed using descriptive statistics (Median, interquartile range) and compared using non-parametric tests (Mann-Whitney U test) and using the chi-square for dichotomous variables. Comparisons within groups were performed using the Kruskal-Wallis test which can be used to determine if there are statistically significant differences between two or more samples. A p value <0.05 was considered statistically significant.

In order to predict the effect on the LUTS bother of different factors studied, we used a mixed model analysis. A mixed model is used when there are multiple groups or panel of individuals and one or more fixed or random variables which can vary across whatever grouping is present.

To test the pertinence of these models, the Akaike information criteria (AIC) were used.

It is a fined technique based on in-sample fit to estimate the likelihood of a model to predict/estimate the future values. AIC can be used to perform model comparisons.

A good model, which means the one with the best predictive performance, is the one that has minimum AIC among all the other models.

Different models have been created with a combination of explanatory variables to describe the bother. The different models have been evaluated and the final model structures proposed in Table 5 and 6 return the overall lowest AIC.

Univariate linear regression analysis was performed to determine associations between the bother and diuresis during daytime and the bother and diuresis during nighttime in different groups of patients depending on the level of general bother (general bother was calculated as the average of bother day and bother night).

RESULTS

During the timeframe of the study, a total of 107 patients with a median age of 59 (20-83) years were included. 43 patients were men (40%) and 64 were women (60%). A total of 320 daytime and 320 nighttime periods from the bladder diaries were studied (1 missing data).

The descriptive data and the correlation of scores obtained from questionnaires relative LUTS-related bother during both day and night are reported in **Table 1** and **Table 2**

BOTHER & SYMPTOMS

We observed a statistically significant difference when studying scores and subscores of symptoms specific questionnaire. Patients with more LUTS -related bother demonstrated higher scores on ICIQ questionnaires. During daytime, the average score of the storage subscore in women was 8 in the group with strong bother

whereas it was 3 in the group with no/mild bother ($p<0.001$); during nighttime, the average of the emptying subscore was 11 in the group of men with moderate bother whereas it was 3 in the group with no/mild bother ($p=0.006$). Women with strong bother during nighttime and daytime had respectively an average ICIQ OAB score of 9.5 and 8, and those with no/mild bother had respectively 4 and 2 ($p<0.001$).

The subscore concerning filling phase in men (ICIQ MLUTS filling phase) and women (ICIQ FLUTS filling phase) were higher when more bother was experienced (statistically significant) during daytime and nighttime, ICIQ MLUTS emptying phase and ICIQ FLUTS Incontinence were not during nighttime. Results are reported in Tables 1 and 2.

A relationship between LUTS-related bother, sleep quality and QoL was found. Participants expressing strong bother during daytime had a PSQI score of 8 whereas in the group of patients with no/mild bother the score was 5 ($p<0.001$). During nighttime, the scores were respectively 9 and 5 ($p<0.001$).

BOTHER & VOIDING DIARY

Comparison of results derived from bladder diaries during daytime and nighttime and sub-classified according to LUTS-associated bother are summarized in **Table 3**.

During daytime, participants with moderate LUTS-associated bother (group2) showed a fluid intake of 1850 mL and those without or with mild bother (group 1) drank an average of 1640mL ($p=0.007$). For nighttime, fluid intake in patients with strong bother was 1815mL versus 1640mL in patients from group 1 ($p=0.024$).

During daytime, patients from group with the more bother had a urine production of 87,3mL/hour whereas those with less complaints had a urine production of 71.27mL/hour ($p<0.001$).

The mean voided volume, during daytime, was respectively 206, 180 and 150mL in groups 1, 2 and 3 ($p<0.001$) and 300, 250 and 171.75 for nighttime ($p<0.001$). This difference was also significant for the night period ($p<0.001$).

The evaluation of voiding diaries revealed that the lower the maximal voided volume was, the more bother the participants experienced ($p=0.028$ during daytime and $p<0.001$ at night).

During daytime, the diurnal bladder capacity was higher in patients experiencing more bother ($p<0.001$).

The nocturia index was significantly higher in patients with more bother ($p<0.001$).

These results show the implication of diuresis in bother related to LUTS.

MIXED MODELS

Mixed model analysis of bother during daytime and nighttime: **Table 4**

The model generated for the evaluation of LUTS bother during daytime had six randomization stratification variables: age, body mass index (BMI), PSQI, ICIQ filling phase score, ICIQ emptying phase score, daytime diuresis.

During daytime, from the mixed model used to assess 6 factors, only two of them were revealed as having an influencing on the bother experienced by male patients: daytime diuresis and ICIQ filling phase score (respectively $p=0.018$ and $p=0.026$). For women, only the ICIQ FLUTS filling score was found as influencing factor ($p<0.001$).

The model generated for the evaluation of LUTS bother during nighttime had six randomization stratification variables: age, body mass index (BMI), PSQI, ICIQ filling phase score, ICIQ emptying phase score, nighttime diuresis.

During nighttime, the mixed model revealed 2 factors with a significant influence on the bother in women: ICIQ FLUTS filling score ($p<0.001$) and nocturnal diuresis ($p=0.005$).

No significant influence were found during nighttime for men.

Mixed model analysis:

The Akaike information criterion (AIC) of the given set of data was 458.579 for men and 719.148 for women during daytime and respectively 416.999 and 675.429 for nighttime bother, confirming these models were superior to the alternative models tested.

Mixed model focused on filling phase: Table 5

The model generated for the evaluation of LUTS bother during daytime had seven randomization stratification variables: gender, age, body mass index (BMI), stress incontinence, PSQI, daytime urine production and maximal voided volume. Only two variables were revealed as having an influencing on the bother experienced by the patient: daytime diuresis and PSQI score (respectively $p=0.007$ and $p=0.012$).

The model generated for the evaluation of LUTS bother during nighttime had seven randomization stratification variables: gender, age, body mass index (BMI), stress incontinence, PSQI, nighttime urine production and maximal voided volume. Four variables significantly predicted bother: gender (female) ($p=0.020$), PSQI ($p=0.003$), greater diuresis ($p<0.001$) and maximum voided volume ($p=0.018$).

Mixed model analysis:

The Akaike information criterion (AIC) of the given set of data for daytime and nighttime bother were respectively 1215.053 and 1123.128, which means that these models were superior to the other alternative models tested.

DISCUSSION

This study has shown that scores of both symptom-specific and quality of life questionnaires were correlated with severity of urinary bother. The more bother the patient experienced, the worst score (s)he reported. Overall women were disproportionately represented in both the moderate and high bother groups. This supports the finding of Hannestad et al. [4] who reported that in women with incontinence, severity of bother was a strong predictor of health care seeking. Any incontinence or evidence of overactive bladder were assessed as being bothersome. However, there was no gender difference in the impact of LUTS as measured by the N-QoL or SF-36.

A feature of this study was the sub-classification of LUTS- related bother and subsequent analysis by day and night bladder parameters. The bladder diary variables indicated that during the day individuals with high LUTS-

related bother demonstrated the lowest maximum and routine storage capacity, yet despite evidence of a significantly higher diuresis had not moderated fluid intake. Similarly during the night, both a lower than expected storage component and an elevated urine production rate were significantly related to moderate or more problematic bother. We explored the possibility that the way the kidneys work, through the diuresis rate, could influence the urinary symptoms experienced by the patient. Patients with increased diuresis rate experienced more bother than the others. Our data suggests that an increase of diuresis of 100mL / h increases bother; by one point in both genders when elevated at night and by a single point in men when raised during the day. Even though this statement is commonly accepted, and makes sense to patients and professional care givers, to our knowledge, this is the first study to assess the effect of diuresis on urinary bother.

An increase in fluid intake was also associated with more severe bother. This confirms the data from studies stressing that decreasing fluids improved symptoms in women with urine incontinence [5] and in patients with overactive bladder symptoms [6], and that to the contrary, increased fluid intake worsen symptoms. Fluid intake is logically directly involved in urine production rate, however drinking habits are influenced by many factors. Thirst, mouth breathing at night, osmole content of diet, beliefs about beneficial effect of high water intake, medication side effects and specific medical conditions all impact an individual's drinking pattern. Diuresis is also influenced by co-existing disease, such as diabetes mellitus, lower limb venous insufficiency, congestive heart failure and dehydration. Thus both fluid intake and urine production rate are affected by multifactorial events, meaning that LUTS-related bother is attributable to both a direct and indirect variables.

There are different possible explanations which could explain the effect of diuresis on urinary bother. There may be a mechanic impact of urine on lower urinary tract function, with water consumption and subsequent diuresis influencing the pattern of urodynamic parameters and micturition. [7].

While there is no consensus in the literature that urinary composition such as its pH or osmolality could affect micturition pattern, some data suggest that micturition in adults is influenced by urinary composition[8,9]. One of the main kidneys' function is to maintain the optimal composition of blood, filtering extra water and toxins. Urine composition may substantially change in different physiological and pathophysiological circumstances. Consequently pH and osmolality may also vary; factors known to alter sensitivity to urgency via a direct effect on the epithelium. In the same way that caffeine can act as a bladder irritant perhaps more concentrated urine is inhospitable and self-limits bladder storage. Finally, since it has been shown that urinary composition changes between kidneys and bladder [10]. Urothelial impermeability may influence sensory threshold in the bladder and the subsequent motor response. It is interesting to note that normative participants in this study routinely voided at volumes well below normal sensation.

The urinary bladder clearly plays a role in LUTS-related bother. The lower the maximal voided volume and/or mean voided volume, the more bother the participants described. This likely coincides with greater urinary frequency and more episodes of threatened continence if the individual is far from a toilet. Bladder index is a derived term that expresses the number of full bladders that a person is generating either during the day or at night. Both the diurnal bladder capacity index (day diuresis / maximal bladder capacity during day) and the

nocturnal bladder capacity index (Nighttime diuresis divided by the maximal bladder capacity during nighttime) significantly increased with LUTS-related bother. This concept is easily understood by patients when for example explaining the mixed aetiology of their symptoms.

The bladder diary was used extensively in this study since it is a non-invasive measurement method to assess diagnostic criteria of LUTS. Its use is recommended in routine clinical practice with feasibility, reliability and validity having been established [11,12]. Whilst there are some limitations in patient collection of urine and documentation of precise times of drinking and micturition, at this point the diary is the gold standard measure of bladder function. Unfortunately it appears to be under used in the daily practice of urologists and general practitioners.

Use of the Pittsburgh Sleep Quality Index is relatively new in urology. Low scores in LUTS patients have drawn attention to the implications of loss of sleep on bladder function. PSQI is a self-rated questionnaire and an interesting tool to assess nocturnal disturbances but also daytime dysfunction through excessive daytime sleepiness [13]. Most notably recent findings have indicated that nocturic episodes related to increased nocturnal diuresis occur during the initial periods of deep sleep, and have a negative effect on energy levels and function during the day. In this study sleep impairment was greater when patients were more bothered by their nLUTS. The PSQI scores were similar for bother related to both day and night LUTS. Our findings are consistent with results from Bliwise et al. [14] who studied 757 patients and showed that patients having to wake up early in the night to void had a high score of PSQI, meaning a poor sleep quality. Poor sleep is both a cause and an effect of awakenings during the night to urinate. The mixed aetiology of LUTS is again highlighted by the level of both expressed in relation to both day and night LUTS.

The clinical implications of the study findings suggest that multiple dysfunctions are contributing to patient perception of the bother related to their LUTS. The clinical outcomes most commonly measured before and after treatment of LUTS are the number of times a person voids (or wakes to go to the toilet) and the number or weight of incontinence pads they use. Using this paradigm there is likely to be lack of concordance between patient and clinician assessment of the impact of LUTS on function and quality of life. The impact of LUTS on quality of life from the patient's perspective is often missed in routine assessment, potentially leading to incorrect selection of patient goals and inappropriate reassessment. When evaluating patients with urinary symptoms it appears relevant to separate daytime from nighttime symptoms, in order to offer an individually tailored management. This is particularly relevant as Bright et al. [15] found a strong association between diary and ICIQ Questionnaires responses regarding nocturia,

Modelling LUTS-related bother in this study confirmed that diuresis rate during the day was an independent predictor in both men and women. This supports the use of bladder diaries alongside medical history-taking as a means of identifying possible causes of increased diuresis before instituting bladder training or pharmacotherapy for day LUTS. Identification of elevated diuresis during the sleeping hours and the contribution of factors altering urine production is crucial in patients with nocturnal LUTS. Our model showed overnight urine production rate, sleep quality and bladder storage to be independent predictors of high bother in both men and

women. This supports the collection of non- lower urinary tract parameters during a routine clinical encounter and the use of open ended questions to identify unmet needs and optimize adherence to intervention.

Generalizability of study findings is limited by sample size and referral center bias. Patients were attending a tertiary center hospital which mean that they are not representative of all patients with LUTS. More severe symptoms or rare clinical features are likely in the population studied. In addition the patients, while not consulting a clinician about their bothersome LUTS, were not entirely free of bladder symptoms. Nonetheless findings conclusively support a multifactorial aetiology for LUTS-related bother. This study links fluid intake and diuresis rates with LUTS, a relationship that seem obvious but has not hitherto been proven. Fluid management is a low-cost and easy to perform measure, with rapid impact.

CONCLUSION

This is the first study evaluating LUTS-associated bother during daytime and nighttime, with a special focus on diuresis rate. We showed that not only bladder and prostate disorders need to be addressed when evaluating and treating LUTS, but also urine production has to be taken into account. Diuresis can vary, depending upon drinking habits, hydration rate, or even pathological situation. Once medical conditions are attended, there is a potential role for fluid manipulation as a non-invasive lifestyle measure, in patients with bothersome LUTS. This study highlights the importance of a holistic and multidisciplinary approach in LUTS patients, even for symptoms which may appear to be restricted to lower urinary tract.

TABLE 1: Descriptive characteristics according to the different groups of bother for daytime and scores retrieved from questionnaires.

Presentation	GROUP 1* No/ mild bother			GROUP 2* Moderate bother				GROUP 3* Strong bother				General comparison p- value
Bother scale	0	1	2	3	4	5	6	7	8	9	10	
DAYTIME BOTHER												
Nb of 24h registrations	220 (68,8%)			56 (17,5%)				44 (13,8%)				
Man n(%)	104 (47,3%)			21 (37,5%)				4 (9,1%)				
Woman n(%)	116 (52,7%)			35 (62,5%)				40 (90,9%)				
Age (years) median (1°Q-3°Q)	55 (43-64,7)			56 (42-7)				49,5 (41,25-61,2)				

BMI° (kg/m²) median (1°Q-3°Q)	24,78 (22,0-28,3)	26,71 (22,1-30,8)	24,03 (21,1-26,9)	
Women				
ICIQ FLUTS storage	3 (2-5)	7 (6-10)	8 (5,5-9)	<0,001
ICIQ FLUTS emptying	0 (0- 2)	2 (1- 6)	3 (1- 5)	<0,001
ICIQ FLUTS incontinence	2 (0-8,25)	8 (2,75-9)	7 (1-8)	0,001
ICIQ OAB	2 (1-5)	7,5 (5,7-9,2)	8 (7-9)	<0,001
Men				
ICIQ MLUTS storage	2 (1-3)	3 (2-4,5)	3,5 (1,5-6,25)	<0,001
ICIQ MLUTS emptying	7 (3- 10)	4 (3- 11)	8 (1,2-13,2)	0,963
ICIQ MLUTS incontinence	3,5 (1-6,2)	5 (2,5-6,5)	10 (7,5-17,7)	<0,001
ICIQ OAB	4 (2-6)	6 (4,5-8,5)	7 (7-10,75)	<0,001
Both genders				
ICIQ nQOL	40 (33,7- 43)	33 (23-39)	29,5 (25,7-32,7)	<0,001
PSQI	5 (3-7)	7 (5- 11)	8 (6,5- 11,5)	<0,001
SF-36 General health	65 (50-80)	50 (35-65)	50 (30-70)	<0,001

°BMI= Body Mass Index

TABLE 2: Descriptive characteristics according to the different groups of bother for nighttime and scores retrieved from questionnaires.

Presentation	GROUP 1*			GROUP 2*				GROUP 3*				General comparison p- value
	No/ mild bother			Moderate bother				Strong bother				
Bother scale	0	1	2	3	4	5	6	7	8	9	10	
NIGHTTIME BOTHER												
Nb of 24h registrations	177 (53,3%)			93 (29,1%)				50 (15,6%)				
Men n(%)	88 (49,7%)			30 (32,3%)				11 (22,0%)				
Women n(%)	89 (50,3%)			63 (33,0%)				39 (78,0%)				
Age (years) median (1°Q-3°Q)	54 (42-64,5)			56 (43-65)				50 (42-64)				

BMI° (kg/m²) median (1°Q-3°Q)	24,78 (21,7-27,6)	26,71 (23,9-30,4)	23,96 (21,1-3,6)	
Women				
ICIQ FLUTS storage	4 (2-6,7)	7 (4,5-7,5)	10 (8,5-14,5)	<0,001
ICIQ FLUTS emptying	1 (0- 2)	2 (0,5- 4,5)	5,5 (1,75- 9,0)	<0,001
ICIQ FLUTS incontinence	4 (0,2-8,7)	8 (0-9)	7,5 (1,75-10)	0,338
ICIQ OAB	4 (2-6,7)	6 (4,5-9)	9,5 (8-12)	<0,001
Men				
ICIQ MLUTS storage	2 (1-3)	4 (4-5)	.	<0,001
ICIQ MLUTS emptying	6 (2,75- 10)	11 (5- 16)	.	0,006
ICIQ MLUTS incontinence	4 (1-6)	7 (5-9)	.	0,020
ICIQ OAB	4 (2-6)	7 (6-9)	.	<0,001
Both genders				
ICIQ nQOL	39 (33-43)	31 (28-35)	22 (18-31)	<0,001
PSQI	5 (3-7)	8 (5-11)	9 (6-13)	<0,001
SF-36 General health	65 (50-80)	47,5 (40-55)	32,5 (17,5-55)	<0,001

* An average bother score has been calculated from the 3 days before the repartition in 3 groups. °Bonferroni- correction: level of significance: from $p < 0,017$

TABLE 3: Comparison of voiding diaries data among the different groups of bother

Presentation	GROUP 1*			GROUP 2*				GROUP 3*				General comparison p- value
	No/ mild bother			Moderate bother				Strong bother				
Bother scale	0	1	2	3	4	5	6	7	8	9	10	
DAYTIME BOTHER												
MVV (mL) Daytime	300 (200-450)			300 (200-400)				232,5 (190-350)				
Intake (mL) 24h	1640 (1262,5-2075)			1850 (1485-2240)				1800 (1500-2192,5)				0.007

Diuresis (mL/h) Daytime Average 3 days	71,27 (51,81-86,00)	80,54 (62,03-110,47)	87,30 (70,10-116,67)	<0.001
Mean voided volume (mL) Average (daytime)	206 (150-280)	180 (133,33-241,25)	150 (100,68-190,94)	<0.001
Diurnal bladder capacity index	2,500 (1,758-3,489)	3,675 (2,529-4,794)	4,3269 (2,886-5,869)	<0.001
NIGHTTIME BOTHER				
MVV (mL) Nighttime	355 (252,5-500)	350 (252,5-490)	255 (180-327,5)	<0.001
Intake (mL) 24h	1640 (1295,5-2120)	1870 (1500-2200)	1815 (1560-2410)	0.024
Diuresis (mL/u) Nighttime	62,58 (42,86-88,50)	83,22 (56,25-121,21)	70,00 (52,72-96,61)	0.001
Mean voided volume (mL) Average (nighttime)	300 (225-450)	250 (162,29-366,25)	171,75 (109,17-228,7)	<0.001 <0.001
Nocturia index**	1,04 (1,00-1,83)	1,93 (1,39-2,42)	2,26 (1,60-3,78)	<0,001
Nocturnal polyuria index	33,09 (23,01-42,33)	37,07 (27,18-50)	36,44 (21,02-44,22)	0,044

*Diurnal bladder capacity index = Daytime diuresis/maximal bladder capacity during daytime

**Nocturia index = Nighttime diuresis/maximal bladder capacity during nighttime

TABLE 4: Mixed model analysis of bother during daytime and nighttime.

	DAYTIME				NIGHTTIME			
	MAN		WOMAN		MAN		WOMAN	
	p-value	β^2	p-value	β^2	p-value	β^2	p-value	β^2
Age	0,83	-0,01	0,16	0,03	0,84	-0,00	0,48	0,02
BMI (kg/m ²)	0,96	-0,00	0,91	-0,01	0,95	0,00	0,17	-0,10
PSQI	0,17	0,16	0,23	0,10	0,87	0,01	0,22	0,12
ICIQ MLUTS or FLUTS								
Filling phase	0,03	0,71	<0,00	0,53	0,17	0,36	<0,00	0,55
Emptying phase	0,09	-0,19	0,62	-0,052	0,56	0,05	0,81	-0,03

Diuresis (daytime/nighttime) (mL/u)	0,02	0,01	0,57	0,00		0,06	0,01	0,01	0,01
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TABLE 5: Mixed model analysis of bother during daytime and nighttime with special emphasis on filling phase.

	p-value	β^2		p-value	β^2
	DAYTIME BOTHER			NIGHTTIME BOTHER	
Gender					
Woman	0,38	0		0,02	0
Man		-0,47			-1,28
Age	0,52	0,01		0,95	-0,00
BMI (kg/m ²)	0,49	0,04		0,91	-0,01
Stress incontinence*					
Yes	0,07	0		0,46	0
No		-1,01			0,41
PSQI ^{oo}	0,01	0,18		0,00	0,21
Diurese (daytime/nighttime) (mL/u)	0,01	0,01		<0,00	0,02
Max. voided volume (24h) (mL)	0,141	-0,00		0,02	-0,00

Authors contributions

All listed authors meet ICMJE <http://www.icmje.org/> authorship criteria.

Nobody who qualifies for authorship has been excluded. Credit for authorship should be based on: [1] substantial contributions to research design, or the acquisition, analysis or interpretation of data; [2] drafting the paper or revising it critically; [3] approval of the submitted and final versions. Authors should meet all three criteria.)

Author1: Concept/design, Data analysis/interpretation, Drafting article, Critical revision of article, Approval of article, Statistics, Data collection.

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Appendix: Overview of study parameters

Parameter	Definition
Intake	Total volume of beverages ingested. In mL
Diuresis	Volume of urine produced during a period of time. In mL/h
Sleeping hours	The time from when an individual goes to bed with the intention of sleeping until they awaken with the intention of rising
Mean voided volume	The mean voided volume passed in a 72-hour period
Maximum voided volume (MVV)	The single largest voided volume passed in a 72-hour period
Nocturnal urine volume (NUV)	Nighttime diuresis. Total volume of urine produced during sleeping hours; includes the first morning void volume
Nocturia index (Ni)	NUV/MVV ; a $Ni > 1$ indicates that NUV exceeds functional bladder capacity and nocturia or enuresis occurs
Nocturnal urine production (NUP)	$NUV/(\text{Sleeping hours})$; $NUP \geq 90\text{mL/h}$ indicates nocturnal polyuria
24-hour total urine volume (TUV)	Total volume of urine passed in a 24-hour period

Nocturnal polyuria index (NPI)	NUV/TUV; NPI > 0.20-0.33 (age-dependent) may be used as an alternative criterion for nocturnal polyuria
Diurnal bladder capacity index	Daytime diuresis/MVV during daytime
ICIQ FLUTS ICIQ MLUTS	International Consultation on Incontinence modular Questionnaire. Self –administered questionnaire in order to assess LUTS in women (ICIQ-FLUTS) and in men (ICIQ-MLUTS).
ICIQ -OAB	Self –administered questionnaire in order to assess more specifically storage symptoms (overactive bladder).
ICIQ-nQoL	Self –administered questionnaire in order to assess quality of life in patient with nocturia.
PSQI	Pittsburgh Sleep Quality Index

TABLE 1: Descriptive characteristics according to the different groups of bother for daytime and scores retrieved from questionnaires.

Presentation	GROUP 1*			GROUP 2*				GROUP 3*				General comparison p- value
Bother scale	0	1	2	3	4	5	6	7	8	9	10	
DAYTIME BOTHER												
Nb of 24h registrations	220 (68,8%)			56 (17,5%)				44 (13,8%)				
Man n(%)	104 (47,3%)			21 (37,5%)				4 (9,1%)				
Woman n(%)	116 (52,7%)			35 (62,5%)				40 (90,9%)				
Age (years) median (1°Q-3°Q)	55 (43-64,7)			56 (42-7)				49,5 (41,25-61,2)				
BMI° (kg/m²) median (1°Q-3°Q)	24,78 (22.0-28,3)			26,71 (22,1-30,8)				24,03 (21,1-26,9)				
Women												<0,001 <0,001 0,001 <0,001
ICIQ FLUTS storage	3 (2-5)			7 (6-10)				8 (5,5-9)				
ICIQ FLUTS emptying	0 (0- 2)			2 (1- 6)				3 (1- 5)				
ICIQ FLUTS incontinence	2 (0-8,25)			8 (2,75-9)				7 (1-8)				
ICIQ OAB	2 (1-5)			7,5 (5,7-9,2)				8 (7-9)				
Men												<0,001 0,963 <0,001 <0,001
ICIQ MLUTS storage	2 (1-3)			3 (2-4,5)				3,5 (1,5-6,25)				
ICIQ MLUTS emptying	7 (3- 10)			4 (3- 11)				8 (1,2-13,2)				
ICIQ MLUTS incontinence	3,5 (1-6,2)			5 (2,5-6,5)				10 (7,5-17,7)				
ICIQ OAB	4 (2-6)			6 (4,5-8,5)				7 (7-10,75)				
Both genders												<0,001 <0,001 <0,001
ICIQ nQOL	40 (33,7- 43)			33 (23-39)				29,5 (25,7-32,7)				
PSQI	5 (3-7)			7 (5- 11)				8 (6,5- 11,5)				
SF-36 General health	65 (50-80)			50 (35-65)				50 (30-70)				

°BMI= Body Mass Index

TABLE 2: Descriptive characteristics according to the different groups of bother for nighttime and scores retrieved from questionnaires.

Presentation	GROUP 1*			GROUP 2*				GROUP 3*				General comparison p- value
Bother scale	0	1	2	3	4	5	6	7	8	9	10	
NIGHTTIME BOTHER												
Nb of 24h registrations	177 (53,3%)			93 (29,1%)				50 (15,6%)				
Men n(%)	88 (49,7%)			30 (32,3%)				11 (22,0%)				
Women n(%)	89 (50,3%)			63 (33,0%)				39 (78,0%)				
Age (years) median (1°Q-3°Q)	54 (42-64,5)			56 (43-65)				50 (42-64)				
BMI° (kg/m²) median (1°Q-3°Q)	24,78 (21,7-27,6)			26,71 (23,9-30,4)				23,96 (21,1-3,6)				
Women												<0,001 <0,001 0,338 <0,001
ICIQ FLUTS storage	4 (2-6,7)			7 (4,5-7,5)				10 (8,5-14,5)				
ICIQ FLUTS emptying	1 (0- 2)			2 (0,5- 4,5)				5,5 (1,75- 9,0)				
ICIQ FLUTS incontinence	4 (0,2-8,7)			8 (0-9)				7,5 (1,75-10)				
ICIQ OAB	4 (2-6,7)			6 (4,5-9)				9,5 (8-12)				
Men												<0,001 0,006 0,020 <0,001
ICIQ MLUTS storage	2 (1-3)			4 (4-5)				.				
ICIQ MLUTS emptying	6 (2,75- 10)			11 (5- 16)				.				
ICIQ MLUTS incontinence	4 (1-6)			7 (5-9)				.				
ICIQ OAB	4 (2-6)			7 (6-9)				.				
Both genders												<0,001 <0,001 <0,001
ICIQ nQOL	39 (33-43)			31 (28-35)				22 (18-31)				
PSQI	5 (3-7)			8 (5-11)				9 (6-13)				
SF-36 General health	65 (50-80)			47,5 (40-55)				32,5 (17,5-55)				

* An average bother score has been calculated from the 3 days before the repartition in 3 groups. °Bonferroni- correction: level of significance: from $p < 0,017$

TABLE 3: Comparison of voiding diaries data among the different groups of bother

Presentation	GROUP 1*			GROUP 2*				GROUP 3*				General comparison p- value
Bother scale	0	1	2	3	4	5	6	7	8	9	10	
DAYTIME BOTHER												
MVV (mL) Daytime	300 (200-450)			300 (200-400)				232,5 (190-350)				0.028
Intake (mL) 24h	1640 (1262,5-2075)			1850 (1485-2240)				1800 (1500-2192,5)				0.007
Diuresis (mL/h) Daytime Average 3 days	71,27 (51,81-86,00)			80,54 (62,03-110,47)				87,30 (70,10-116,67)				<0.001
Mean voided volume (mL) Average (daytime)	206 (150-280)			180 (133,33-241,25)				150 (100,68-190,94)				<0.001
Diurnal bladder capacity index	2,500 (1,758-3,489)			3,675 (2,529-4,794)				4,3269 (2,886-5,869)				<0.001
NIGHTTIME BOTHER												
MVV (mL) Nighttime	355 (252,5-500)			350 (252,5-490)				255 (180-327,5)				<0.001
Intake (mL) 24h	1640 (1295,5-2120)			1870 (1500-2200)				1815 (1560-2410)				0.024
Diuresis (mL/u) Nighttime	62,58 (42,86-88,50)			83,22 (56,25-121,21)				70,00 (52,72-96,61)				0.001
Mean voided volume (mL) Average (nighttime)	300 (225-450)			250 (162,29-366,25)				171,75 (109,17-228.7)				<0.001 <0.001
Nocturia index**	1,04 (1,00-1,83)			1,93 (1,39-2,42)				2,26 (1,60-3,78)				<0.001
Nocturnal polyuria index	33,09 (23,01-42,33)			37,07 (27,18-50)				36,44 (21,02-44,22)				0,044

*Diurnal bladder capacity index = Daytime diuresis/maximal bladder capacity during daytime

**Nocturia index = Nighttime diuresis/maximal bladder capacity during nighttime

TABLE 4: Mixed model analysis of bother during daytime and nighttime.

	DAYTIME				NIGHTTIME			
	MAN		WOMAN		MAN		WOMAN	
	p-value	β^2	p-value	β^2	p-value	β^2	p-value	β^2
Age	0,83	-0,01	0,16	0,03	0,84	-0,00	0,48	0,02
BMI (kg/m ²)	0,96	-0,00	0,91	-0,01	0,95	0,00	0,17	-0,10
PSQI	0,17	0,16	0,23	0,10	0,87	0,01	0,22	0,12
ICIQ MLUTS or FLUTS								
Filling phase	0,03	0,71	<0,00	0,53	0,17	0,36	<0,00	0,55
Emptying phase	0,09	-0,19	0,62	-0,052	0,56	0,05	0,81	-0,03
Diuresis (daytime/nighttime) (mL/u)	0,02	0,01	0,57	0,00	0,06	0,01	0,01	0,01

TABLE 5: Mixed model analysis of bother during daytime and nighttime with special emphasis on filling phase.

	p-value	β^2		p-value	β^2
	DAYTIME BOTHER			NIGHTTIME BOTHER	
Gender					
Woman	0,38	0		0,02	0
Man		-0,47			-1,28
Age	0,52	0,01		0,95	-0,00
BMI (kg/m ²)	0,49	0,04		0,91	-0,01
Stress incontinence*					
Yes	0,07	0		0,46	0
No		-1,01			0,41
PSQI ^{oo}	0,01	0,18		0,00	0,21
Diurese (daytime/nighttime) (mL/u)	0,01	0,01		<0,00	0,02
Max. voided volume (24h) (mL)	0,141	-0,00		0,02	-0,00

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