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Nocturnal Excretion in Healthy Older Women and Rationale for a Safer Approach to Sleep Disruption

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Abstract

Background: Insomnia, especially difficulty maintaining sleep, is prevalent among older adults and increases the incidence of falls and fractures. Moreover, the drugs used to treat it exacerbate the risk. Yet current therapies fail to address one of its most common causes in older adults: nocturia and its primary contributor--nocturnal polyuria (NP)--especially among the majority of individuals without lower urinary tract symptoms (LUTS). Therefore, we examined the factors associated with nocturia in two groups of such older women and the impact of nocturia on sleep.

Design: Secondary analysis of two observational studies of bladder function in carefully-evaluated healthy older women

Setting: Academic medical center

Participants: Thirty-nine women without LUTS who had adequate fluid intake (i.e., >1200 ml urine output/24 hours recorded on their diary), normal videourodynamic testing, and normal daytime frequency (≥ 7 voids).

Measurements: Voided volumes and sleep duration obtained from subjects' 3-day voiding diary, and sleep quality from Center for Epidemiologic Studies Depression Scale. Nighttime excretion of >33% of 24-hour urine volume was considered NP.

Results: Twenty-one of these healthy subjects (54%) awakened at least once nightly to void and 19 (90%) of them had NP. Compared to those without nocturia, participants with nocturia had shorter duration of first uninterrupted sleep period (182 ± 100 vs. 250 ± 60 minutes, $p=.03$), and reported worse sleep quality. Two factors contributed independently to nocturia: 1) a larger proportion of 24-hour urine output at night (43.4 ± 7.4 vs. $25.4 \pm 5.5\%$, $p<.001$) and 2) smaller bladder capacity (484 ± 157 vs. 608 ± 167 ml, $p=.02$).

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Conclusions: Nocturia, NP, and reduced bladder capacity are very common even in healthy older women without LUTS and are associated with impaired sleep. Thus, applying currently available modalities to address *both* NP *and* reduced bladder capacity may effectively treat sleep disruption without incurring the complications of sedative hypnotics.

Keywords

Insomnia; Nocturia; Nocturnal polyuria; Older adults; Sleep

INTRODUCTION

Insomnia is common and problematic, especially among older adults.¹ Difficulty maintaining sleep increases with age and affects 40-70% of older adults.^{2,3} In addition to its adverse impact on quality of life, insomnia confers an increased risk for falls and fractures,^{4,5} and the risk is further exacerbated by the sedative/hypnotics used to treat it.⁶⁻⁸ Although most research has focused on developing more effective pharmacological and behavioral approaches to insomnia, much less attention has been devoted to identifying and addressing other possible contributors to sleep disruption among older adults, the group most likely to suffer and the one most susceptible to experience the resulting morbidity. Two such contributors include nocturia and bladder dysfunction, especially in those who lack lower urinary tract symptoms (LUTS).

Nocturia is one of the most common causes of sleep disruption in older adults.⁹ It is defined as waking at least once nightly to void, with each void preceded and followed by sleep.¹⁰ Three-quarters of surveyed Americans cite the need to go to the bathroom as the most frequent reason for nocturnal awakenings.⁹ Thus, nocturia and insomnia are inextricably linked and it may be difficult to discern clinically whether nocturia is a cause or consequence of insomnia, especially in older adults in whom comorbidity and polypharmacy are common.¹¹

To address this issue, we conducted a secondary analysis of two previously-completed studies of older women without LUTS to determine: (1) nocturnal voiding patterns; (2) the prevalence of bladder dysfunction, nocturia, and NP; and (3) the interplay between sleep and these bladder dysfunctions.

METHODS

Study Design

We examined baseline participant data derived from two prospective studies of healthy and continent older women. One study examined normative voiding patterns in carefully-screened healthy older adults, and the other assessed brain responses to bladder filling in a similar group.¹²⁻¹⁴

Participants

Subjects were cognitively intact, functionally independent, community-dwelling women aged 60 and older without LUTS as defined below. The study was approved by the

University of Pittsburgh institutional review board, and all participants provided written informed consent.

Both studies excluded women with a history of conditions that may affect LUT function, including bladder cancer, spinal cord lesions, multiple sclerosis, pelvic radiation, interstitial cystitis, urethral obstruction, urinary retention (PVR > 200 ml after non-instrumented void), clinically apparent past or current neurological diseases, and those who were medically unstable.

Clinical Assessment

All participants had completed a comprehensive baseline evaluation which included complete medical and voiding history, and a detailed physical examination (including neurological, cognitive and stress testing).

All participants also underwent comprehensive videourodynamic testing^{15,16} to exclude involuntary bladder contractions (detrusor overactivity) and other significant bladder dysfunction such as impaired contractility, compliance, outlet obstruction, and sphincter dysfunction. Methods and definitions conformed to those of the International Continence Society.¹⁷

The 3-day bladder diary completed by participants at baseline was used in this secondary analysis. Because intake had not been recorded, we used 24-hour excretion volumes as a proxy for fluid intake. Diary records included the times and volumes of each void, as well as the actual times subjects awoke and went to sleep each day. The first void after waking for the day was included in the nocturnal urine volume (NUV). The nocturnal polyuria index (NPi) was calculated by dividing NUV by 24-hour urine volume; nocturnal polyuria (NP) was defined by an NPi > 33%.¹⁸ Participants with a 24-hour urine volume >40 ml/kg body-weight were classified as having 24-hour polyuria.¹⁰ Time in bed was defined as the interval between going to bed with the intent of sleeping and getting up for the day, and was obtained using times recorded in the bladder diary.

The short form of the Center for Epidemiologic Studies Depression Scale (CES-D) was completed at baseline by a subset of participants. Because the primary focus of the parent studies was assessment of voiding function, there were no specific sleep-related questionnaires and so we used the sleep restlessness question of the CES-D as a proxy measure of sleep quality. The question assessed sleep restlessness over the past few weeks. Scores ranged from 0 to 3 for having sleep restlessness rarely (<1 day), some of the time (2-3 days), occasionally (3-4 days), or all of the time (5-7 days). Given the small number of participants, we operationally combined those with a score of 0 or 1 as having good sleep and those with scores of 2 or 3 as having poor sleep.

Since the analysis was performed on participant data from two studies, to standardize our cohort we included only participants who met the following definition of “normal”: 1) denied precipitant urgency and incontinence on both detailed questioning and questionnaire, 2) had normal results on videourodynamic testing, 3) had adequate but not excessive fluid

intake (i.e. 1200- 2500 ml urine output/24 hours by 3-day voiding diary), and 4) had normal daytime frequency (≤ 7 voids).¹⁹

Statistical Analysis

Independent sample t-test and chi-square test were used to compare continuous and categorical characteristics respectively. Pearson correlation coefficients (r) and corresponding p-values were used to quantify the strength of associations between continuous variables. For participants with available CES-D scores, we compared NPi, duration of uninterrupted sleep, and the volume of the first nocturnal void across the two self-rated categories of sleep quality using independent samples t -tests. Statistical significance was set at $\alpha=0.05$ and all analyses were performed using SAS® version 9.3 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Thirty-nine women met our definition of “normal”. Subject characteristics are summarized in Table 1. Age ranged from 60-87. Participants were all continent, active, functionally-independent community-dwelling older women without peripheral edema or bladder overactivity. Despite these characteristics, as well as having normal daily output and daytime frequency, more than half of these participants had nocturia (54%) which was attributable to NP in 90% of them.

Subjects with nocturia were somewhat older, but BMI, medication profile, nutritional status, and renal function were comparable in those with and without nocturia (Table 1).

Although daytime frequency was similar between those with and without nocturia, women with nocturia had significantly smaller functional bladder capacity, and their mean voided volume while awake was 41% less compared to women without nocturia (Table 2). Notably, 24-hour urine volume was also significantly *less* in the group with nocturia.

NPi correlated with increasing age ($r=.37$, $p=.02$) higher BMI ($r=.38$, $p=.05$), longer time in bed ($r=.5$, $p=.001$), and shorter duration of first uninterrupted sleep period before first awakening to void ($r=-.58$, $p=.001$).

Nocturia and Sleep

Overall, subjects with nocturia spent nearly an hour more in bed than those without nocturia; 60% spent >8 hours in bed per night. However, NP was not only related to time in bed but also to the duration of uninterrupted sleep (DUS) before the first awakening to void; those with NP had an hour less DUS than did those without NP. Participants with a shorter DUS reported worse sleep quality and had a higher NPi although time in bed was not significantly different. (Fig. 1)

DISCUSSION

Despite their good health, normal daily fluid intake and daytime frequency, normal videourodynamic testing, and lack of precipitant urgency, 54% of our participants had

nocturia. Our study highlights two important findings: (1) even among this group of healthy older women without LUTS, those with nocturia had smaller bladder capacity, smaller mean voided volume, and a lower 24-hour urine volume than those without; and (2) nocturics reported poor sleep despite spending more time in bed. NP, the primary etiology of nocturia in older adults,²⁰ was related not only to time in bed but also to poor sleep quality and shorter DUS.

The smaller voided volumes among those with nocturia likely reflects self-induced fluid restriction to avoid daytime frequency; yet NUV, NP_i, and nighttime frequency were higher than in those without nocturia. Equally important, those with nocturia had smaller bladder capacity. Because our evaluation excluded intrinsic LUT pathology, the reduced bladder capacity is likely functional in nature and the result of fluid restriction and frequent volitional voiding. Regardless of the cause, however, reduced bladder capacity can magnify the impact of NP.

Another important contributor to nocturnal voiding frequency in healthy older females is NP. In our study, shorter DUS was associated with poor and restless sleep and higher NP_i. Slow wave sleep or non-rapid eye movement (NREM), often considered the most restorative stage of sleep, predominates in the first 3-4 hours of the night^{21,22} and interruption during NREM leads to impaired alertness and poor mental performance relative to awakenings from other stages.^{21,23} Our findings concur with recent evidence^{24,25} and underscore that shorter DUS is associated with poor sleep quality. Therefore, increasing the duration of uninterrupted sleep should be considered an important therapeutic goal in the treatment of insomnia and nocturia.

In addition to helping delineate the interplay between nocturia, DUS and sleep quality, our findings also provide a useful insight into a novel additional target for the treatment of interrupted sleep: *functional bladder capacity*. Despite having a stable and normally compliant bladder, participants with nocturia had 20% smaller functional bladder capacity than did those without nocturia. This was associated with a 27% decrease in the duration of their first uninterrupted sleep period. Therefore, modalities to increase functional bladder capacity should be considered as a treatment option among those reporting poor and interrupted sleep. Behavioral interventions such as delayed voiding and timed progressive voiding have been shown to increase functional bladder capacity in women with LUTS.²⁶⁻²⁸ An increase of 100 ml in bladder capacity can increase the duration of uninterrupted sleep by more than an hour and hence improve sleep and sleep quality without use of sedative hypnotics.

This study has several strengths. To our knowledge, it is the first study to explore the contributors to nocturia in such a carefully characterized cohort of healthy older women without LUTS. The strict definition enabled us to detect significant differences in bladder diary variables among those with and without nocturia. We also used standardized definitions to categorize our patients for nocturia, NP and other bladder diary variables which further increases the validity of our findings.

Limitations should also be mentioned. First, the sample size is relatively small, which reflected our decision to employ strict inclusion parameters. We wanted to ensure that, although participants denied precipitant urge, they were not compensating for OAB by excess fluid restriction or increased voiding frequency. Yet, to our knowledge, this is the largest group of older individuals without LUTS studied to elucidate the factors associated with nocturia, a prevalent and morbid condition in this age group. Additionally, if nocturia and NP are this common in robustly healthy older adults without LUT pathology, it suggests that our findings may reflect only the tip of the iceberg and NP may be even more prevalent in patients with multiple comorbidities and sleep disruption. Second, our study relies on the accuracy of participants' voiding diaries. However, the frequency volume chart has previously proven to be a reliable and reproducible representation of true voiding function,^{29,30} and all participants were cognitively intact volunteers interested in contributing to research and unaware of our hypothesis. Finally, since the primary studies were not intended or designed to examine sleep duration, or quality of sleep, we used proxy measures to report sleep quality and restlessness. However, our findings concur with recent evidence that links sleep interruption to poor sleep quality.^{24,25}

CONCLUSION

Sleep and nocturia are inextricably linked in older women, even among those who are healthy and free of LUTS. Nocturia is strongly associated with NP, reduced bladder capacity, duration of first uninterrupted sleep period, and reduced sleep quality. Our findings suggest that addressing *both* NP *and* reduced bladder capacity in such individuals may provide an opportunity to improve sleep quality in this population while also eliminating the need for and, more importantly, the risks of sedative hypnotics.

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Figure 1:

Comparing NPi, time in bed, and duration of uninterrupted sleep (DUS) before first awakening to void with sleep restlessness as scored in CES-D questionnaire with scores of 0 or 1 used a proxy for good sleep, and scores of 2 or 3 as proxy for poor sleep

Table 1:

Characteristics of the participants with and without nocturia

Characteristics	All (n=39)	Nocturia (n=21)	No nocturia (n=18)	p-value
Age, yr (sd)	66.5 (6.8)	70 (7.6)	64 (4.6)	.01
BMI, (sd)	25.8 (4.8)	25.1(4.2)	26.5 (5.3)	.38
Smoking, % (n)- None	51 (20)	45 (9)	58 (11)	.44
Past	31 (12)	40 (8)	21 (4)	
Current	8 (3)	10 (2)	5 (1)	
Albumin, (sd)	4.1 0(.3)	4.0 (0.3)	4.2 (0.4)	.11
Creatinine, (sd)	.9 (.8)	.8 (.2)	.79 (.2)	.76
Medication use, % (n)				
ACE/ARB	15 (6)	20 (4)	11 (2)	.41
Thiazide diuretic	10 (4)	15 (3)	5 (1)	.31
CCB	13 (5)	20 (4)	5 (1)	.16
Anti-depressant	13 (5)	10 (2)	16 (3)	.59
NSAIDS	18 (7)	15 (3)	21 (4)	.62
Comorbidities, % (n)				
Cardiovascular	28 (11)	32 (6)	25 (5)	.11
Neurological	5 (2)	5 (1)	5 (1)	.89
Musculoskeletal	56 (22)	63 (12)	50 (10)	.10
Psychiatric	18 (7)	21 (4)	15 (3)	.20

Note: BMI= body mass index, ACE-I/ARB= Angiotensin converting enzyme inhibitor/ Angiotensin receptor blocker CCB= calcium channel blockers, NSAIDS= non-steroidal anti-inflammatory drugs.

Comorbidities: cardiovascular conditions include hypertension, atrial fibrillation, history of congestive heart failure [but not current], or heart attack; neurological conditions include peripheral neuropathy and transient ischemic attack; musculoskeletal conditions include arthritis, osteoporosis, joint replacement; and psychiatric conditions include history of depression and anxiety [but not current]. The Mini-mental score of every subject was >24 (normal).

Table 2:

Bladder-related parameters of the participants with and without nocturia

Characteristics	All (n=39)	Nocturia (n=21)	No nocturia (n=18)	p-value
Nocturia, no. of episodes (sd)	.8 (0.8)	1.2 (0.9)	.4 (0.5)	<.01
No. of subjects with NP	19	19	0	
Frequency while awake (no. of voids)	5.6 (1.2)	5.5 (1.1)	5.7 (1.3)	.70
FBC, ml (sd)	544 (172)	484 (157)	608 (167)	.02
NBC, ml (sd)	508 (165)	474 (149)	584 (177)	.04
Mean voided volume while awake, ml	266 (105)	199 (65)	337 (93)	<.01
24-hr volume, ml (sd)	1885 (644)	1606 (434)	2178 (705)	<.01
24 h polyuria, % (n)	13 (5)	0 (0)	26 (5)	.02
DUV, ml (sd)	1267 (527)	930 (227)	1620 (523)	<.01
NUV, ml (sd)	633 (243)	710 (251)	555(214)	.04
Time in bed, min	512 (81)	545 (95)	487 (55)	.06
DUS, min		182 (100)	250 (60)	.03
NPi, % (sd)	34.6 (11.2)	43.4 (7.4)	25.4 (5.5)	<.01

Note: NP= nocturnal polyuria, FBC= functional bladder capacity, NBC= nocturnal bladder capacity, DUV= diurnal urine volume, NUV= nocturnal urine volume, DUS: duration of uninterrupted sleep, NPi= nocturnal polyuria index (NUV/24-hr volume *100)