



Original Article

Int Neurorol J 2022;26(2):135-143
<https://doi.org/10.5213/inj.2142330.165>
pISSN 2093-4777 · eISSN 2093-6931



Impact of Aging on Urinary Natriuretic Peptides in Nocturia and Nocturnal Polyuria

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Purpose: The pathophysiology of nocturia and nocturnal polyuria (NP), conditions that become more prevalent with aging, may in part be explained by changes in hormones involved in water homeostasis. The purpose of this study was to analyze the impact of aging on urinary natriuretic peptides in nocturia and NP.


Methods: Patients aged ≥ 18 years completed 24-hour bladder diaries for assessment of nocturia and NP. They were divided into subgroups of ≥ 65 years old and < 65 years old. Urine samples were collected and analyzed for natriuretic peptide (NT-proANP, NT-proBNP, and NT-proCNP) levels. Peptide levels were compared between patients with and without nocturia/NP and within age subgroups; correlation to the NP index (NPI) was determined.

Results: Compared to patients without nocturia ($N = 15$), patients with nocturia ($N = 36$) had higher median levels of urinary NT-proANP (15.8 pmol/mmol Cr vs. 10.9 pmol/mmol Cr, $P = 0.016$) and NT-proBNP (6.3 pmol/mmol Cr vs. 4.5 pmol/mmol Cr, $P = 0.021$), but showed no differences in NT-proCNP (2.4 pmol/mmol Cr vs. 2.5 pmol/mmol Cr, $P = 0.967$). Patients ≥ 65 years old with nocturia had higher NT-proANP (29.8 pmol/mmol Cr vs. 11.0 pmol/mmol Cr, $P < 0.001$) and NT-proBNP (9.6 pmol/mmol Cr vs. 5.0 pmol/mmol Cr, $P < 0.001$) than patients < 65 years old. Additionally, patients with NP ($N = 30$) showed higher urinary NT-proANP (19.6 pmol/mmol Cr vs. 10.5 pmol/mmol Cr, $P < 0.001$) and NT-proBNP (6.7 pmol/mmol Cr vs. 4.7 pmol/mmol Cr, $P = 0.020$) compared to patients without NP ($N = 21$). NP patients ≥ 65 years had higher NT-proANP (29.8 pmol/mmol Cr vs. 12.5 pmol/mmol Cr, $P < 0.001$) and NT-proBNP (9.6 pmol/mmol Cr vs. 4.4 pmol/mmol Cr, $P = 0.004$) than patients < 65 years old. NPI positively correlated with urinary NT-proANP ($R_s = 0.417$, $P = 0.002$) and NT-proBNP ($R_s = 0.303$, $P = 0.031$), but not with NT-proCNP ($R_s = -0.094$, $P = 0.510$).


Conclusions: Since urinary NT-proANP and NT-proBNP were greater in aged patients with nocturia and NP, natriuretic peptides may contribute to the pathophysiology of these conditions and further research should aim to explore them as targets for management.

Keywords: Nocturia; Natriuretic peptides; Aging; Lower urinary tract symptoms; Biomarkers

- **Fund/Grant Support:** The study was supported by the Ferdinand C. Valentini Medical Student Research Grant in Urology from the New York Academy of Medicine (awarded to LK).
- **Research Ethics:** This study was approved by the Institutional Review Board & Privacy Board SUNY of Downstate Medical Center (No. 1471991-4). All participants provided informed consent for the study.
- **Conflicts of interest:** LK has no conflict of interests to declare and certifies that any potential conflict of interests for all authors are the following: JPW is a consultant for Ferring and the Institute for Bladder and Prostate Research. All other authors have nothing to disclose.

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Submitted: November 8, 2021 / **Accepted after revision:** December 15, 2021

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INTRODUCTION

Nocturia, defined as waking to pass urine during the main sleep period, with ≥ 2 nighttime voids considered clinically significant, impacts all age groups [1-3]. In a review of 43 articles investigating nocturia prevalence, it was found that the prevalence of nocturia is greater in adults over 70 (68.9%–93%) compared to younger adults ages 20 to 40 (11%–43.9%) [4]. Nocturia has the most significant impact on quality of life amongst lower urinary tract symptoms (LUTS), with nocturia patients self-reporting being tired “always” or “usually” significantly more than patients with daytime only LUTS [5]. While a variety of factors can cause nocturia, nocturnal polyuria (NP), characterized by nocturnal urine volume greater than 20%–33% of 24-hour voided volume, is the major contributing factor [2].

The increased prevalence of nocturia with aging may be in part due to hormonal changes, such as dysregulation of the diurnal rhythm of plasma antidiuretic hormone (ADH) concentration [6]. In healthy adults, there is a physiological increase in plasma ADH concentration during the night which decreases nocturnal diuresis. However, this increase in ADH secretion during the night was observed to be absent in elderly subjects with nocturia [7]. Additionally, V2 ADH receptor expression in urinary bladder mucosa and the kidneys may change with age, contributing to nocturia pathophysiology [8].

Another family of hormones involved in water homeostasis, natriuretic peptides, may also play a role; this family is made up of atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) [9,10]. ANP is secreted from the right atrium in response to stretching of the atrial wall, sensed via atrial volume receptors and comprises most of the total circulating natriuretic peptides. B-type natriuretic peptide (BNP) is secreted from the cardiac ventricular myocytes in response to increased ventricular wall stress. C-type natriuretic peptide (CNP) is secreted from cardiac endothelium in response to shear stress. While the active forms of these hormones have short half-lives, their inactive N-terminal regions, serving as more stable markers, are secreted in similar molar ratios to the active regions and have longer half-lives: NT-proANP (60–120 minutes), NT-proBNP (120 minutes), and NT-proCNP (> 120 minutes) [11-13]. In fact, urinary natriuretic peptides can be markers of heart failure; all are elevated in patients with heart failure, with urinary NT-proBNP having a diagnostic accuracy comparable with that of plasma NT-

proBNP [14].

The purpose of this study is to evaluate the impact of aging on urinary natriuretic peptides in patients with nocturia and NP.

MATERIALS AND METHODS

This study was conducted in accordance with the Declaration of Helsinki guidelines and approved by the Institutional Review Board (IRB) & Privacy Board of SUNY Downstate Medical Center (No. 1471991-4) in November 2019. All participants provided informed consent for the study.

In this IRB approved study, patients 18 years or older who were evaluated across 2 clinics were recruited from November 2019 to July 2021. Following enrollment, participants underwent blood pressure measurements and urine collection. Patients completed 24-hour voiding diaries over 3 consecutive days (72 hours) as part of the assessment of nocturia/NP. Nocturia was defined as ≥ 2 nighttime voids, which was determined clinically significant by the International Consultation on Incontinence Research Society; NP was defined as NP index (NPi; equal to nocturnal urine volume divided by 24-hour urine volume) > 0.33 [3].

Patients were included if they were ≥ 18 years of age. Patients were excluded if they had any comorbidities that may influence nocturia including other urologic conditions (e.g., benign prostatic hyperplasia, overactive bladder, prostate cancer), cardiovascular conditions (e.g., congestive heart failure, coronary artery disease, history of myocardial infarction), metabolic conditions (e.g., diabetes insipidus, hypercalcemia, diabetes mellitus), neurological conditions (e.g., autonomic neuropathy, epilepsy, spinal cord injury), and various other conditions (e.g., obstructive sleep apnea, renal tubular dysfunction). Patients who drank alcohol, were treated with medications impacting urine output (e.g., diuretics, urinary stimulants, alpha agonists/blockers), and had past urologic surgeries (e.g., prostatectomy, transurethral resection of the prostate, urethroplasty) were also excluded.

Patients were categorized by status of nocturia/NP and subdivided into age groups (≥ 65 years and < 65 years) to follow the model of previous studies [4]. Baseline characteristics retrieved included age, gender, nighttime voids, body mass index, systolic and diastolic blood pressures, and creatinine levels (serum and urine). Urine samples following the first morning void were collected from patients and stored at -20°C ; they were thawed out at 4°C for analysis. Measurement of urinary NT-

proANP (Product by Biomedica, Vienna, Austria; purchased through Eagle Biosciences, Amherst, NH, USA), NT-proBNP (BioVendor, Asheville, NC, USA), and NT-proCNP (Product by Biomedica, Vienna, Austria; purchased through Eagle Biosciences, Amherst, NH, USA) for all patients was done using commercially designed enzyme-linked immunoassay kits following standard protocol. All urinary natriuretic peptide measurements were adjusted for creatinine excretion by dividing urine natriuretic peptide concentration (pmol/L) by urine creatinine concentration (mmol/L); adjusted values were used for statistical analysis.

Data on baseline characteristics and urinary natriuretic peptide levels was reported as median and interquartile range (IQR). The Mann-Whitney U-test was used to compare patients with and without nocturia/NP; additionally, chi-square analysis was done for gender differences. For analysis on age, the 4 groups (defined by presence or absence of nocturia/NP and age ≥ 65 years or < 65 years) were compared using the Kruskal-Wallis H-test for overall significance, followed by the Mann-Whitney U-test to determine differences between specific subgroups. Scatter plots of urinary natriuretic peptides vs

age were made for the 4 subgroups. Spearman rank order correlation was used to determine the correlation between urinary natriuretic peptides and age for the 4 subgroups and NPi and urinary natriuretic peptides for the overall patient population. Level of statistical significance was set at $P < 0.05$. All analyses were done via IBM SPSS Statistics ver. 27.0 (IBM Co., Armonk, NY, USA).

RESULTS

Baseline characteristics of all 51 patients are provided in Table 1. Compared to patients without nocturia (N = 15), patients with nocturia (N = 36) had significantly higher median levels of urinary NT-proANP and NT-proBNP, but showed no differences in median NT-proCNP. The same relationships were observed for patients with NP (N = 30) compared to patients without NP (N = 21). In addition, patients with NP had higher median NPi compared to patients without NP (median [IQR]: 0.44 [0.12] vs. 0.18 [0.05], $P < 0.001$).

Impact of aging on nocturia was compared by analyzing differences between patients younger than 65 years (N = 6 for no

Table 1. Baseline characteristics and urinary natriuretic peptide levels in nocturia and nocturnal polyuria

Variable	Nocturia			Nocturnal polyuria		
	Absent (N = 15)	Present (N = 36)	P-value	Absent (N = 21)	Present (N = 30)	P-value
Age (yr)	68.0 (8.0)	64.0 (13.8)	0.084	64.0 (7.0)	64.0 (7.8)	0.611
Sex, n (%)			0.650			0.687
Male	6 (40.0)	12 (33.3)		7 (33.3)	11 (36.7)	
Female	9 (60.0)	24 (66.7)		14 (66.7)	19 (63.3)	
Body mass index (kg/m ²)	28.2 (3.4)	29.3 (5.5)	0.226	29.2 (7.1)	28.9 (4.0)	0.389
Systolic blood pressure (mmHg)	126.0 (14.0)	134.0 (18.8)	0.612	135.0 (17.0)	131.0 (18.0)	0.333
Diastolic blood pressure (mmHg)	76.0 (3.5)	79.5 (11.0)	0.106	78.6 (6.0)	78.5 (13.5)	0.559
Serum creatinine (mg/dL)	0.9 (0.3)	0.9 (0.2)	0.126	0.8 (0.2)	0.9 (0.3)	0.985
Urine creatinine (mg/dL)	55.0 (10.5)	56.0 (8.8)	0.481	55.0 (9.0)	56.0 (8.8)	0.591
Nighttime voids	1.0 (0)	2.5 (2.0)	$< 0.001^*$	1.0 (1.0)	3.0 (2.0)	$< 0.001^*$
Nighttime volume (mL)	300.0 (237.5)	587.5 (481.3)	$< 0.001^*$	290.0 (100.0)	675.0 (385.0)	$< 0.001^*$
Total volume (mL)	1,550.0 (265.0)	1,500.0 (885.0)	0.780	1,500.0 (320.0)	1,600.0 (956.3)	0.343
NT-proANP (pmol/mmol Cr)	10.9 (5.8)	15.8 (19.5)	0.016*	10.5 (5.8)	19.6 (18.1)	$< 0.001^*$
NT-proBNP (pmol/mmol Cr)	4.5 (2.4)	6.3 (5.0)	0.021*	4.7 (2.6)	6.7 (6.5)	0.020*
NT-proCNP (pmol/mmol Cr)	2.5 (0.7)	2.4 (0.4)	0.967	2.5 (0.7)	2.3 (0.4)	0.646

Values are presented as median (interquartile range) unless otherwise indicated.

NT-proANP, N-terminal proatrial natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide; NT-proCNP, N-terminal pro C-type natriuretic peptide.

* $P < 0.05$, statistically significant differences.

Table 2. Urinary natriuretic peptide levels in patients younger and older than 65 years with nocturia

Group	Age < 65 years	Age ≥ 65 years	P-value
NT-proANP (pmol/mmol Cr)			
No nocturia	11.3 (3.8)	10.5 (5.6)	0.689
Nocturia	11.0 (7.5)	29.8 (9.3)	<0.001*
NT-proBNP (pmol/mmol Cr)			
No nocturia	2.9 (0.8)	5.0 (1.3)	0.008*
Nocturia	5.0 (4.4)	9.6 (4.8)	<0.001*
NT-proCNP (pmol/mmol Cr)			
No nocturia	2.8 (0.6)	2.5 (0.6)	0.607
Nocturia	2.4 (0.3)	2.3 (0.5)	0.804

Values are presented as median (interquartile range). NT-proANP, N-terminal proatrial natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide; NT-proCNP, N-terminal pro C-type natriuretic peptide; Cr, creatinine. *P < 0.05, statistically significant differences.

nocturia and N = 24 for nocturia) and older than or equal to 65 years (N = 9 for no nocturia and N = 12 for nocturia) (Table 2). Kruskal-Wallis H-test comparing the 4 subgroups showed significant differences for urinary NT-proANP (P < 0.001) and NT-proBNP (P < 0.001), but not NT-proCNP (P = 0.902). Patients ≥ 65 years old with nocturia had higher median urinary NT-proANP (29.8 pmol/mmol Cr vs. 11.0 pmol/mmol Cr, P < 0.001) and NT-proBNP (9.6 pmol/mmol Cr vs. 5.0 pmol/mmol Cr, P < 0.001) levels than those < 65 years old; in addition, older patients with nocturia also had higher median NT-proANP (29.8 pmol/mmol Cr vs. 10.5 pmol/mmol Cr, P < 0.001) and NT-proBNP (9.6 pmol/mmol Cr vs. 5.0 pmol/mmol Cr, P < 0.001) levels than those without nocturia. Patients ≥ 65 years old without nocturia also had higher median NT-proBNP levels than those < 65 years old (P = 0.008).

The impact of aging on NP was also analyzed comparing patients aged less than 65 years (N = 12 for no NP and N = 18 for NP) and greater than or equal to 65 years (N = 9 for no NP and N = 12 for NP) (Table 3). Kruskal-Wallis H-test comparing the 4 subgroups showed significant differences for urinary NT-proANP (P < 0.001) and NT-proBNP (P = 0.001), but not NT-proCNP (P = 0.734). Patients ≥ 65 years old with NP had higher median NT-proANP (29.8 pmol/mmol Cr vs. 12.5 pmol/mmol Cr, P < 0.001) and NT-proBNP (9.6 pmol/mmol Cr vs. 4.4 pmol/mmol Cr, P = 0.004) than patients < 65 years old with NP; older patients with NP also had higher median NT-proANP (29.8

Table 3. Urinary natriuretic peptide levels in patients younger and older than 65 years with nocturnal polyuria

Group	Age < 65 years	Age ≥ 65 years	P-value
NT-proANP (pmol/mmol Cr)			
No nocturnal polyuria	9.6 (5.4)	10.5 (5.6)	0.995
Nocturnal polyuria	12.5 (7.8)	29.8 (9.3)	<0.001*
NT-proBNP (pmol/mmol Cr)			
No nocturnal polyuria	4.0 (3.6)	5.0 (1.3)	0.219
Nocturnal polyuria	4.4 (4.8)	9.6 (4.8)	0.004*
NT-proCNP (pmol/mmol Cr)			
No nocturnal polyuria	2.6 (0.5)	2.5 (0.6)	0.554
Nocturnal polyuria	2.4 (0.3)	2.3 (0.5)	0.602

Values are presented as median (interquartile range). NT-proANP, N-terminal proatrial natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide; NT-proCNP, N-terminal pro C-type natriuretic peptide; Cr, creatinine. *P < 0.05, statistically significant differences.

pmol/mmol Cr vs. 10.5 pmol/mmol Cr, P < 0.001) and NT-proBNP (9.6 pmol/mmol Cr vs. 5.0 pmol/mmol Cr, P < 0.001) than those without NP. Data on urinary natriuretic peptides, not adjusted for urinary creatinine excretion, is available in supplement Tables 1-3.

Age positively correlated with urinary NT-proANP (R_s = 0.613, P < 0.001) and NT-proBNP (R_s = 0.396, P = 0.017) for the patients with nocturia and with urinary NT-proBNP (R_s = 0.485, P < 0.001) for patients without nocturia (Fig. 1). When analyzing NP, age positively correlated with urinary NT-proANP (R_s = 0.610, P < 0.001) and NT-proBNP (R_s = 0.386, P = 0.035) for patients with NP (Fig. 2). NP_i positively correlated with urinary NT-proANP (R_s = 0.417, P = 0.002) and NT-proBNP (R_s = 0.303, P = 0.031), but did not correlate with NT-proCNP (R_s = -0.094, P = 0.510).

DISCUSSION

Natriuretic peptides play an important role in water homeostasis, ranging from increasing excretion of salt and water to increasing vasodilation in order to decrease blood pressure and cardiac stress [6,9,10]. Due to their ability to impact urination, we hypothesized that they likely play a role in the pathophysiology of nocturia and NP. Previous studies have demonstrated the involvement of ANP in nocturia; for example, in patients with sleep apnea experiencing nocturia, fluctuations of intra-

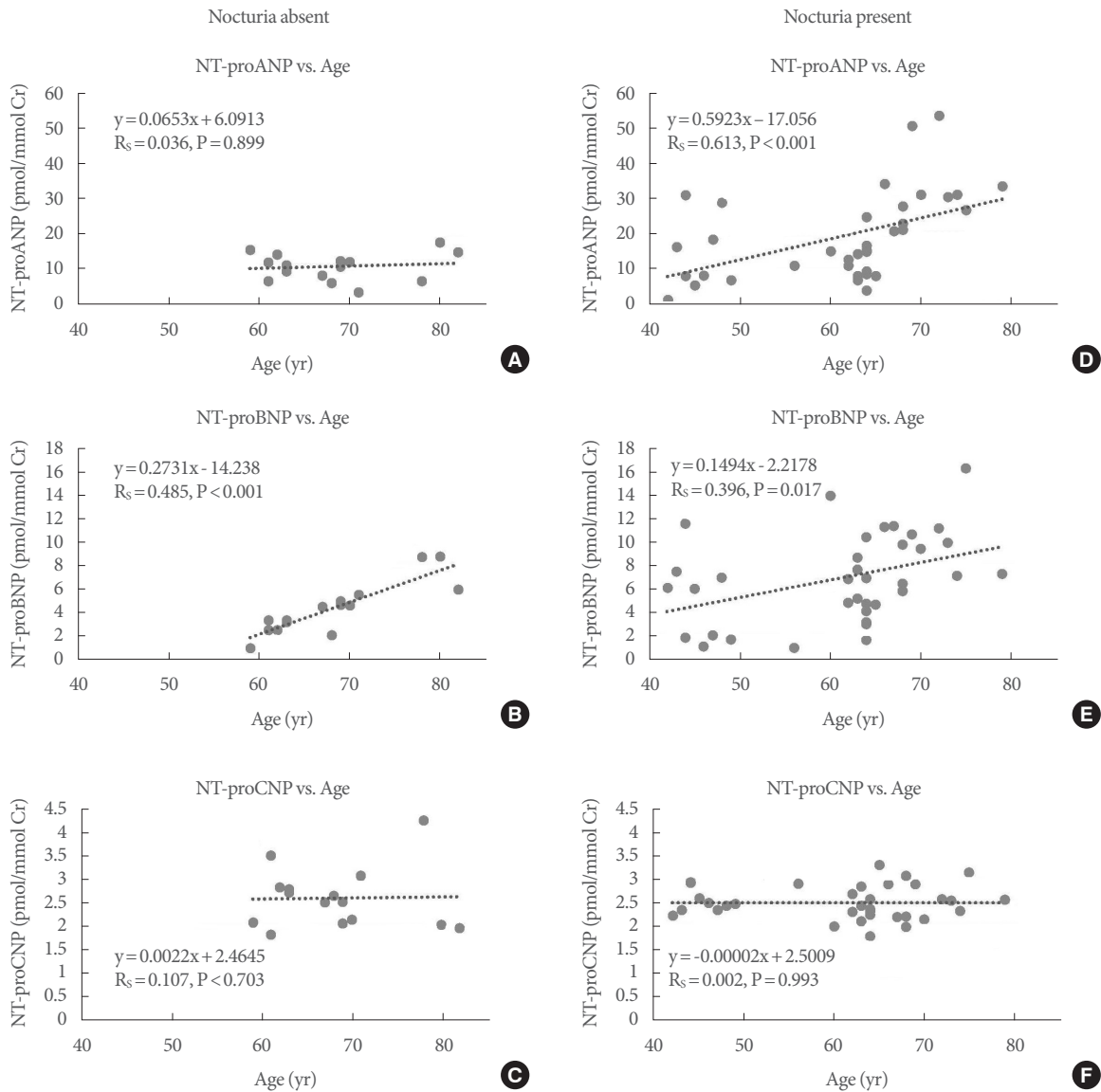


Fig. 1. Scatter plots and spearman correlations between urinary natriuretic peptides (NT-proANP, NT-proBNP, and NT-proCNP) and age for patients without nocturia (A-C) and patients with nocturia (D-F). R_s , Spearman rank order correlation coefficient; NT-proANP, N-terminal proatrial natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide; NT-proCNP, N-terminal pro C-type natriuretic peptide; Cr, creatinine.

thoracic pressures were correlated to fluctuations in levels of ANP, potentially explaining the development of nocturia [15-17]. Nevertheless, to the best of our knowledge, the levels of natriuretic peptides, especially using urine samples, have not been investigated in patients with nocturia and NP in relation to age. In the present study, higher urinary levels of NT-proANP and NT-proBNP were noted in patients with nocturia/NP, potentially leading in part to increased nighttime voiding. These results were expected as both ANP and BNP are involved with

natural diuresis physiologically and are in tandem with previous findings in studies relating both to sleep apnea [15-19]. NT-proCNP, a peptide that has not been studied before in nocturia patients, showed no differences between patients with and without nocturia/NP. Physiologically, CNP has various cardiovascular functions similar to other natriuretic peptides and also plays a role in bone growth, neuronal development, and reproduction; lack of differences in CNP was not expected due to its role in natriuresis [20].

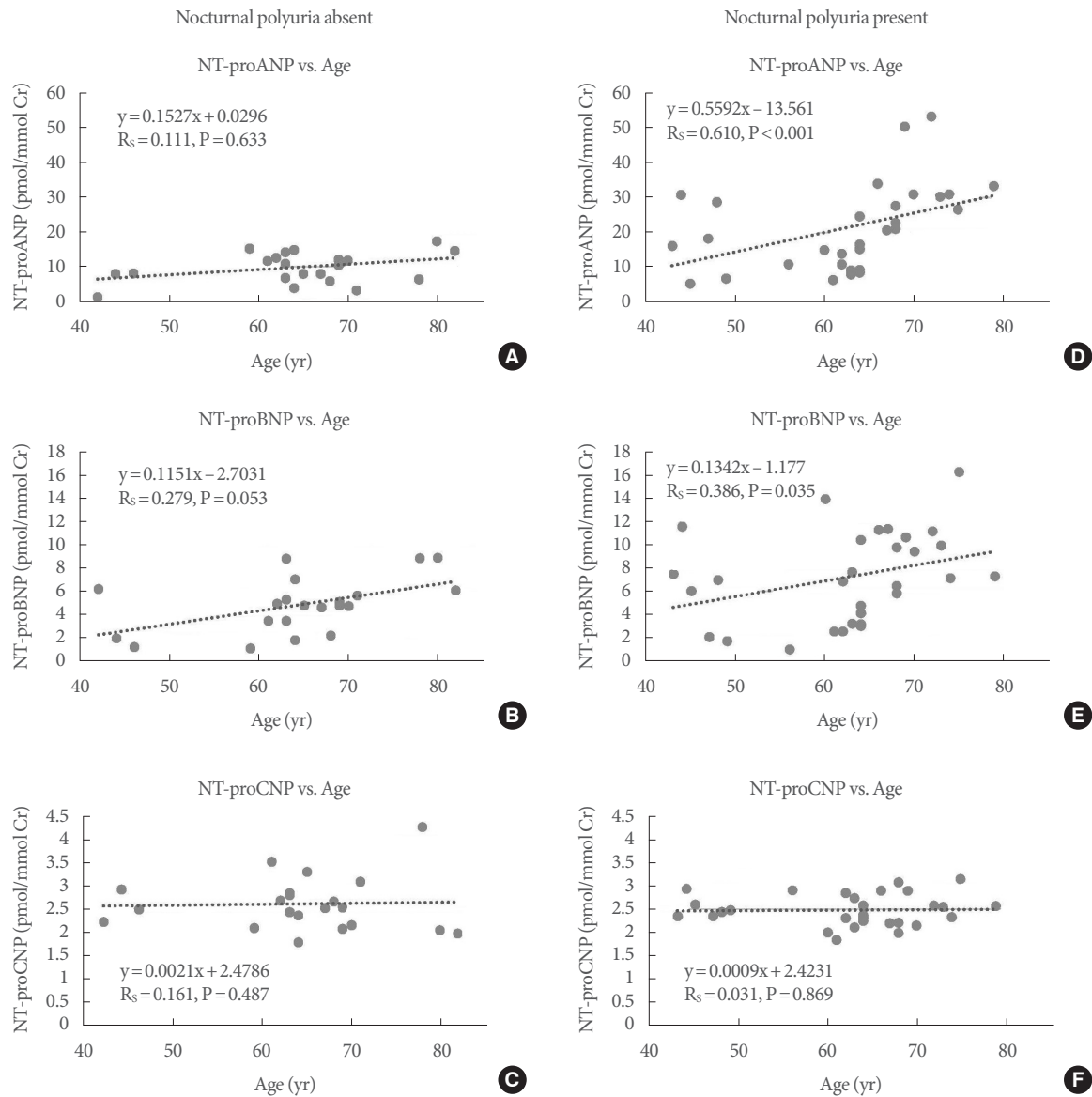


Fig. 2. Scatter plots and spearman correlations between urinary natriuretic peptides (NT-proANP, NT-proBNP, and NT-proCNP) and age for patients without nocturnal polyuria (A-C) and patients with nocturnal polyuria (D-F). R_s , Spearman rank order correlation coefficient; NT-proANP, N-terminal proatrial natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide; NT-proCNP, N-terminal pro C-type natriuretic peptide; Cr, creatinine.

Age-related changes to hormones involved in water homeostasis have also been associated with nocturia. For example, studies have shown ADH, which in normal individuals peaks at night to reduce urine output by 25%, is insufficiently secreted in the elderly with nocturia [21]. Our study shows that age and natriuretic peptide levels are also related in nocturia/NP. Urinary NT-proANP was almost 2.4–2.9 times greater in elderly patients with nocturia/NP compared to those younger than 65 years old. Analysis of the urinary NT-proBNP shows that in

both patients with and without nocturia, the levels almost doubled in the older group; this effect was retained only for patients with NP. In addition, correlations between age and urinary NT-proANP and NT-proBNP were noted for the nocturia and NP groups. A previous cross-sectional analysis supports our results because it also showed an association between increased serum NT-proBNP and nocturia [22]. No impact of aging was noted on urinary NT-proCNP levels.

Since older patients without nocturia had higher NT-proBNP

than younger patients, there is a possibility that other factors are contributing to the pathophysiology of nocturia; these could include hormones and other biomolecules, age-related LUT dysfunction, or other underlying conditions not accounted for. Future research should be done to investigate additional factors associated with water homeostasis in the context of nocturia development. Another possibility is that there is a clinical threshold below which differences in BNP levels do not influence nocturia development, which can be determined with larger scale prospective studies. However, there were no differences found in NT-proBNP levels in older vs younger patients without NP, suggesting that BNP may be playing a stronger role in nocturia development as a result of NP rather than other potential etiologies.

Nocturia is highly prevalent in patients with heart failure and while mechanisms remain unclear, they may be due to direct effects of heart failure (e.g., increased peripheral lower extremity edema redistributing when laying supine at night or release of natriuretic peptides from cardiac cells) or the use of diuretics [23]. In our analysis, we excluded all patients with heart failure to explore potential alternate causes of nocturia/NP that may be in part due to changes in natriuretic peptides. In the absence of heart failure, natriuretic peptides have been noted to increase due to various etiologies ranging from left/right ventricular hypertrophy, right ventricular dysfunction from pulmonary diseases, inflammatory diseases, and endocrine disease [24]. Since we excluded many of these disease states, we believe that reason for the higher urinary natriuretic peptides noted in nocturia/NP, with the effects increasing with aging, are likely due to LV hypertrophy and remodeling, which commonly also occurs with aging, causing greater release of the peptides; these changes are likely modulated by blood pressure increases and further explorations of the correlations between age-related nocturia/NP and natriuretic peptides when stratified by status of hypertension are warranted [25].

Several limitations exist for our study. Due to the smaller sample size of the study and patients being from the same medical center, findings are underpowered and would require further support from larger multi-center studies. Also, while we used extensive exclusion criteria, participants may have had comorbidities not accounted for that impacted findings. Data may have been prone to operator error when running the procedure to detect peptide levels; however, by running the procedure twice with the use of standards and controls, we tried to reduce this error. A lack of measurements of plasma ADH and natri-

uretic peptides limited our assessment of the pathophysiology of nocturia/NP; further research should look to assess plasma measurements to provide additional insight. We also did not measure prostate size or PSA; although, by excluding disease states like benign prostatic hyperplasia/LUTS and prostate cancer, there was no indication for these measurements.

Despite these limitations, to the best of our knowledge, we are the first study to compare urinary natriuretic peptides in patients with nocturia/NP and provide analysis on the impact of age. Urinalysis of natriuretic peptides provides the benefit of less invasive testing over plasma studies and convenience of adding the measurement as part of the urinalysis for other analytes commonly done for patients with nocturia to understand underlying disease. An exploration of the correlations of urinary natriuretic peptides to other urinary analytes may provide further insight on nocturia pathophysiology. In separately analyzing NP rather than singularly examining nocturia in the absence of other nocturia causing etiologies, we aimed to show that specific mechanistic differences may exist that impact development of NP. Experimentation and data analysis was performed by separate individuals, reducing bias. By using voiding diaries to determine presence of nocturia, we abided by standardized protocol and therefore removed any self-reporting error. Overall, the study demonstrates that urinary NT-proANP and NT-proBNP levels are higher in nocturia and greater levels can be seen in patients ≥ 65 years old. While studies have suggested measuring plasma levels of these hormones for evaluation of cardiovascular conditions, this study opens the possibility to monitor these hormones via urinalysis to evaluate nocturia. Further work should look to use preclinical study designs in controlled settings to establish causality. Another future direction of this study is to observe the relationship of these hormones in the setting of nocturia while accounting for hypertension. Hypertension is commonly associated with nocturia and with natriuretic peptides impacting blood pressure, it is important to understand their relationship to effectively treat patients. Understanding the underlying pathophysiology of nocturia can aid development of treatment pathways, which can be targeted to specific age demographics.

Natriuretic peptides may play a role in the pathophysiology of nocturia and NP, serving as markers for the condition. Urinary NT-proANP and NT-proBNP were greater in patients with nocturia/NP compared to patients without nocturia/NP, and differences increased with age. Urinary NT-proCNP was not different amongst patients. These findings suggest that hor-

monal changes play a role in the pathophysiology of nocturia/NP with aging and should be used to guide further preclinical studies in controlled settings to establish causality. Nevertheless, our results demonstrate potential for developing treatment pathways unique to managing nocturia and NP in aging patients.

AUTHOR CONTRIBUTION STATEMENT

- Conceptualization: LK, JPW, LAB
- Data curation: LK, JUB, JS, SNR, DJG, MWM, YA, AA, JML, JPW, LAB
- Formal analysis: LK, JUB, JS, SNR, DJG, MWM, YA, AA, JML, JPW, LAB
- Funding acquisition: LK, JPW, LAB
- Methodology: LK, JUB, JS, SNR, DJG, MWM, YA, AA, JML, JPW, LAB
- Project administration: LK, JPW, LAB
- Visualization: LK, JUB
- Writing-original draft: LK, JUB, JS, SNR, DJG, MWM, YA, AA, JML, JPW, LAB
- Writing-review & editing: LK, JUB, JS, SNR, DJG, MWM, YA, AA, JML, JPW, LAB

SUPPLEMENTARY MATERIALS

Supplementary Tables 1-3 can be found via <https://doi.org/10.5213/inj.2142330.165>.

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REFERENCES

1. Hashim H, Blanker MH, Drake MJ, Djurhuus JC, Meijlink J, Morris V, et al. International Continence Society (ICS) report on the terminology for nocturia and nocturnal lower urinary tract function. *Neurourol Urodyn* 2019;38:499-508.
2. Weiss JP, Everaert K. Management of nocturia and nocturnal polyuria. *Urology* 2019;133S:24-33.
3. Denys MA, Cherian J, Rahnama'i MS, O'Connell KA, Singer J, Wein AJ, et al. ICI-RS 2015-Is a better understanding of sleep the key in managing nocturia? *Neurourol Urodyn* 2018;37:2048-52.
4. Bosch JL, Weiss JP. The prevalence and causes of nocturia. *J Urol* 2013;189(1 Suppl):S86-92.
5. Everaert K, Anderson P, Wood R, Andersson FL, Holm-Larsen T. Nocturia is more bothersome than daytime LUTS: Results from an Observational, Real-life Practice Database including 8659 European and American LUTS patients. *Int J Clin Pract* 2018;72:e13091.
6. Birder LA, Van Kerrebroeck PEV. Pathophysiological mechanisms of nocturia and nocturnal polyuria: the contribution of cellular function, the urinary bladder urothelium, and circadian rhythm. *Urology*. 2019;133S:14-23.
7. Asplund R, Aberg H. Diurnal variation in the levels of antidiuretic hormone in the elderly. *J Intern Med* 1991;229:131-4.
8. Birder LA, Wolf-Johnston AS, Jackson EK, Wein AJ, Dmochowski R. Aging increases the expression of vasopressin receptors in both the kidney and urinary bladder. *Neurourol Urodyn* 2019;38:393-7.
9. Curry FR. Atrial natriuretic peptide: an essential physiological regulator of transvascular fluid, protein transport, and plasma volume. *J Clin Invest* 2005;115:1458-61.
10. Kerkelä R, Ulvila J, Magga J. Natriuretic peptides in the regulation of cardiovascular physiology and metabolic events. *J Am Heart Assoc* 2015;4:e002423.
11. Yagmur E, Scaer JH, Koek GH, Weiskirchen R, Trautwein C, Koch A, et al. Elevated MR-proANP plasma concentrations are associated with sepsis and predict mortality in critically ill patients. *J Transl Med* 2019;17:415-2.
12. Weber M, Mitrovic V, Hamm C. B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide - Diagnostic role in stable coronary artery disease. *Exp Clin Cardiol* 2006;11:99-101.
13. Kuehnl A, Pelisek J, Bruckmeier M, Safi W, Eckstein HH. Comparative measurement of CNP and NT-proCNP in human blood samples: a methodological evaluation. *J Negat Results Biomed* 2013;12:7.
14. Ng LL, Geeranavar S, Jennings SC, Loke I, O'Brien RJ. Diagnosis of heart failure using urinary natriuretic peptides. *Clin Sci (Lond)* 2004;106:129-33.
15. Ouslander J, Johnson T, Nasr S, Schnelle J, Miller M. Atrial natriuretic peptide levels in geriatric patients with nocturia and nursing home residents with nighttime incontinence. *J Am Geriatr Soc* 1999;47:1439-44.
16. Umlauf MG, Chasens ER, Greevy RA, Arnold J, Burgio KL, Pillion DJ. Obstructive sleep apnea, nocturia and polyuria in older adults. *Sleep* 2004;27:139-44.
17. Yalkut D, Lee LY, Grider J, Jorgensen M, Jackson B, Ott C. Mechanism of atrial natriuretic peptide release with increased inspiratory resistance. *J Lab Clin Med* 1996;128:322-8.

18. Yoshimura K, Nakayama T, Sekine A, Matsuda F, Kosugi S, Yamada R, et al. B-type natriuretic peptide as an independent correlate of nocturnal voiding in Japanese women. *Neurourol Urodyn* 2012; 31:1266-71.
19. Miyazaki T, Kojima S, Yamamuro M, Sakamoto K, Izumiya Y, Tsujita K, et al. Nocturia in patients with sleep-disordered breathing and cardiovascular disease. *Circ J* 2015;79:2632-40.
20. Lumsden NG, Khambata RS, Hobbs AJ. C-type natriuretic peptide (CNP): cardiovascular roles and potential as a therapeutic target. *Curr Pharm Des* 2010;16:4080-8.
21. Hirayama A, Torimoto K, Yamada A, Tanaka N, Fujimoto K, Yoshida K, et al. Relationship between nocturnal urine volume, leg edema, and urinary antidiuretic hormone in older men. *Urology* 2011;77:1426-31.
22. Okumura K, Obayashi K, Tai Y, Yamagami Y, Negoro H, Kataoka H, et al. Association between NT-proBNP and nocturia among community-dwelling elderly males and females: a cross-sectional analysis of the HEIJO-KYO study. *Neurourol Urodyn* 2021;40:112-9.
23. Redeker NS, Adams L, Berkowitz R, Blank L, Freudenberger R, Gilbert M, et al. Nocturia, sleep and daytime function in stable heart failure. *J Card Fail* 2012;18:569-75.
24. Tsai SH, Lin YY, Chu SJ, Hsu CW, Cheng SM. Interpretation and use of natriuretic peptides in non-congestive heart failure settings. *Yonsei Med J* 2010;51:151-63.
25. Cheng S, Fernandes VR, Bluemke DA, McClelland RL, Kronmal RA, Lima JA. Age-related left ventricular remodeling and associated risk for cardiovascular outcomes: the multi-ethnic study of atherosclerosis. *Circ Cardiovasc Imaging* 2009;2:191-8.