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Does hormonal therapy affect the bladder or the kidney in postmenopausal women with and without nocturnal polyuria: Results of a pilot trial?

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ABSTRACT

Aim: To observe the impact of hormonal treatment (HT) on voiding patterns and renal circadian rhythms in postmenopausal women with and without nocturnal polyuria (NP).
Material and Methods: A prospective, observational study was executed at the menopause clinic of a tertiary hospital. HT was based on patients' choice and was in the form of either oral and transdermal oestrogen. Participants completed a 72-hour bladder diary, completed the ICIQ-FLUTS questionnaire, recorded a renal function profile and gave a blood sample. This set of tests was done before and after 3 months of HT.
Results: 32 postmenopausal women with a median age of 52.5 (49.3–56.0) years were enroled in this study. Three months of HT resulted in a significant decrease in fluid intake ($p < 0.001$) and daytime voiding frequency ($p = 0.019$). No impact on nocturnal parameters was observed. Observations drawn from the questionnaires did not differ between the baseline and three-month assessments.
HT led to a disappearance of the circadian rhythm of the diuresis rate and sodium clearance in patients without NP, as no significant difference between daytime and night-time values was observed (diuresis rate $p = 0.3$; sodium clearance $p = 0.08$). In patients with NP at baseline, HT did not induce a circadian rhythm of the diuresis rate and sodium clearance ($p = 0.2$; $p = 0.7$). In contrast, free water clearance did change to a clear circadian rhythm ($p = 0.02$).
Conclusion: HT led to a significant reduction in both fluid intake and daytime frequency. In women without NP, HT led to a disruption of the circadian rhythms of water and salt diuresis. In patients with NP, a limited normalisation of the circadian rhythm of free water clearance was observed after three months of HT.
Clinical trial registration number from ClinicalTrials.gov: NCT04891926

1. Introduction

Circadian rhythms are defined as important drivers regulating the sleep–wake cycle of multiple internal processes. Urine production is subject to such circadian rhythm, as diuresis and thus urine production should be limited during the night in order to obtain an adequate night-time rest [1]. It is well documented that diuresis is influenced by the stimulation of the Renin-Angiotensin-Aldosterone System (RAAS) and the release of antidiuretic hormone (ADH) which respectively play a role in sodium and water reabsorption. In healthy, young subjects the ADH release during night-time reduces free water clearance (FWC), whereas the hormones of the RAAS and the atrial natriuretic peptide (ANP) are responsible for night-time sodium reabsorption [2,3].

Literature observed that age [4,5] and obesity [6] can influence these circadian rhythms negatively, as blunted or inversed rhythms for sodium and water clearance were observed in older and obese patients. Blunted

Abbreviations: ADH, antidiuretic hormone; ANP, atrial natriuretic peptide; FWC, free water clearance; FVC, frequency volume chart; HT hormonal treatment, HT hormonal treatment; ICS, International Continence Society; IQR, interquartile range; LUTS, lower urinary tract symptoms; NP, nocturnal polyuria; NPI, Nocturnal Polyuria Index; OAC, oral anticonception; RAAS, renin angiotensin aldosterone system; RFP, renal function profile.

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rhythms may have implications, as they lead to a higher nocturnal urine production which can result in nocturia and accompanied sleep disruption [7,8]. In literature, it is suggested that menopause can negatively impact the circadian rhythms of diuresis [9]. However, no consensus regarding the impact of oestrogen and progesterone on the circadian rhythm of ADH and RAAS stimulation has been obtained, although different studies have studied this subject [10–12].

Firstly, Mahler et al. observed in a group of pre - and post–puberty girls that the clear circadian rhythm of sodium clearance observed in the pre-puberty stage was not affected after transition to young adolescent [10]. Forsling et al. observed in a trial including reproductive women that ADH levels were significantly higher at the time of ovulation compared to those at the onset of menstruation, suggesting an impact of oestrogen on ADH release [11]. On the contrary, a Danish study observed no differences in the circadian rhythms of ADH release, diuresis and urinary osmolality in reproductive women between the luteal and midfolliculair phase [12]. In addition, the same author observed a clear circadian rhythm of diuresis, ADH concentrations and sodium clearance [13] in the luteal phase of reproductive women with and without intake of oral anticonception (OAC). A Greek study rebutted these findings, reporting that the night-time increase in ADH release was attenuated in reproductive women using OAC [14]. Lastly, different authors agree on the positive impact of hormonal therapy (HT) on diuresis in postmenopausal women, as a clear night-time rise in ADH concentration were observed, resulting in water retention and a reduced urine output [15–17].

Patients with nocturnal polyuria (NP), defined as an overproduction of urine during night-time [18], generally present with blunted circadian rhythm for sodium and or water clearance leading to an increased nocturnal diuresis [4,19]. Water diuresis is induced through a disabled circadian rhythm of ADH resulting in a low FWC during the night. Salt diuresis is mainly managed by an impaired function of the RAAS or an increased release of ANP which both result in a high sodium clearance during night-time [19]. Due to the presence of those disabled rhythms in patients with NP, this group may serve as an ideal target population to evaluate the impact of estrogens on the circadian rhythms of urine production.

NP is important, as it is considered to be the most common cause of nocturia [7,20]. Nocturia is a typical bothersome voiding dysfunction, which comes along with a significant increase of patients morbidity and mortality [21,22]. Next to NP, nocturia can be provoked by global polyuria, sleep disorders or a reduced bladder capacity [23]. Earlier studies including postmenopausal women with nocturia showed that systemic HT has a positive impact on nocturnal frequency [24,25], whereas vaginal oestrogen has been shown to have low evidence in the treatment of nocturnal frequency [26].

The aim of this research was to observe the impact of HT on voiding patterns and the circadian rhythms of water and salt diuresis in postmenopausal women with and without NP.

2. Material & methods

2.1. Patient selection

This prospective, observational study was executed between January 2015 and June 2017 at the menopause clinic of a tertiary hospital. All postmenopausal women who were proposed to start HT by their physician to treat postmenopausal symptoms (hot flushes, vaginal dryness) were asked to enrol in this trial. Menopausal status was biochemically confirmed (FSH, LH, oestrogen).

2.2. Treatment allocation

Patients were treated with continuously combined systemic HT in the form of oral or transdermal substitution. Treatment form was based on patients' choice. In patients without an earlier hysterectomy, oestrogen treatment was continuously combined with progesterone, as oestrogen only therapy increases the risk of endometrial hyperplasia [27].

2.3. Measurements

Women were asked to complete a 72-hour frequency volume chart (FVC), to collect a renal function profile (RFP) and a blood sample. Moreover, all women were asked to complete the ICIQ-FLUTS questionnaire. This set of tests was conducted twice: once before treatment initiation and once more after 3 months of continuous therapy.

The FVC provides more information concerning micturition and drinking frequency and volumes. Moreover, the time of going to sleep and awakening was questioned. A blood sample was taken to measure sodium and osmolality concentrations and to further calculate sodium and FWC.

The RFP is a 24-hour urine analysis in which urine samples are collected at fixed time points every 3 h, starting 3 h after the first morning void. This RFP was collected on a separated day to the FVC. Daytime samples were taken between 10:00–11:30 (U1), 13:00–15:30 (U2), 16:00–17:30 (U3), 19:00–20:30 (U4), and 22:00–23:30 (U5). The night-time samples were taken between 1:00–2:30 (U6), 4:00–5:30 (U7) and 7:00–8:30 (U8), and the volume of each interim void, was noted to calculate the 24 h, daytime and night-time urine volume and diuresis rate. However, the RFP sampling for determining circadian rhythm took place within variable 90-minute window, in order to have given patients a bit of flexibility on this schedule. Based on this RFP, NP was calculated based on the nocturnal polyuria index (NPI) as proposed by the ICS [18]. Women were divided amongst two groups depending on the presence of NP. On each of this 8 samples, creatinine and sodium were analysed. Subsequently, the renal clearance of creatinine, sodium and solutes (Usubst x Uflow / Psubst) and FWC (urine flow – solute clearance) were calculated.

Lastly, women were asked to complete the female version of the validated questionnaire on LUTS (ICIQ-FLUTS) to assess frequency (0 - 15), voiding (0 - 12) and incontinence symptoms (0 - 20), with 0 being no symptoms.

2.4. Statistical analysis

Statistical analysis was performed using SPSS version 27. The median, interquartile range (IQR) and frequency were recorded as descriptive parameters. The Shapiro-Wilk test was used to identify whether the variables were normally distributed. Baseline differences in FVC, RFP and questionnaires between baseline and after treatment situation were assessed using a paired Wilcoxon signed rank test. The Mann-Whitney U test was used to compare continuous variables at both assessments between women with and without NP. Statistical significance was considered at $p < 0.05$. The study was approved by the institutions review board (EC 2014/1241). Written informed consent was obtained from all participants.

3. Results

3.1. Descriptive statistics

Thirty-two postmenopausal women with a median age of 52.5 (49.3–56.0) years were enroled in this study. Oral treatment was initiated in 84.4% (27/32) of all women. As only 15.6% (5/32) of all involved women used transdermal estrogens, no further stratification per treatment group was done. The median weight was 70 (65–82) kg and the median height was measured at 167 (160–172) cm, corresponding with a median BMI of 25.5 (23.0–28.2) kg/m^2. At baseline, 53% (17/32) of all women suffered from NP. No significant differences amongst baseline characteristics (age, BMI, length and weight) were observed between women with and without NP.

Table 1
Overview of the Frequency Volume Chart (FVC) at baseline and after 3 months of HT for total group, nocturnal polyuria (NP) group and non – NP group.

	No nocturnal polyuria $N = 15$			Nocturnal Polyuria N = 17			Total group $N = 32$		
	Before	After	P – Value*	Before	After	P – Value*	Before	After	P – Value *
Total intake (ml)	2200 (1885–2700)	2000 (1228.3–2193.3)	**0.005**	1891 (1575–2687)	1549.5 (1354–2127.3)	**0.008**	2030 (1650–2700)	1763 (1318–2111)	< **0.001**
Total urine volume (ml)	2385 (2100 −2988)	2257.5 (1625.8–2832.5)	0.5	1771 (1286–2379)	1855 (1528.3 −2235.3)	0.7	2123 (1750–2705)	1954 (1625 - 2590)	0.4
Nocturnal Urine Volume (ml)	600 (500–783)	509.2 (422–792.5)	0.5	607 (493	581.5 (413.8 −712.5)	0.2	600 (500–775)	538 (438 - 758)	0.2
Number of nocturnal voids	1 (0.7–1.7)	0.8 (0.0–1.4)	0.1	1.0 (0.7–1.2)	1.0 (0.3–1.0)	0.3	1 (0.7–1.3)	1 (0–1)	0.056
Mean nocturnal voided volume (ml)	400 (175 - 533)	421.5 (248.5–792.5)	0.2	387.5 (245.8–587.5)	356.5 (219.4–609.4)	0.7	400 (240–550)	384 (243–645)	0.6
Number of daytime voids	8.7 (7.0–9.3)	7.2 (6.5–8.1)	**0.002**	7.7 (7.0–8.7)	7.0 (6.4–8.9)	0.7	7.7 (7 0.0–9.0)	7 (6.6–8.3)	**0.019**
Mean daytime voided volume (ml)	221.8 (184.3–252.4)	240.7 (168.6–317.4)	0.3	165.8 (108.5–195.5)	173.2 (146.7–250.2)	0.3	188 (159–229)	205 (156–263)	0.2

* Comparisons were made using the Wilcoxon–signed–rank test. A p – value < 0.05 was considered significant and highlighted in bold.

3.2. Bladder parameters

3.2.1. Objective bladder parameters

In the total group, 3 months of HT resulted in a significant decrease of fluid intake ($p < 0.001$). Subsequently, a decrease in daytime voiding frequency ($p = 0.019$) was observed, as women tend to have 0.7 daytime voids less after treatment. amongst the total group, no treatment impact on the total urinary output and on the nocturnal parameters could be observed (Table 1).

Baseline FVC parameters were compared between women with and without NP. A significant higher total urinary output was observed in women without NP compared to those with NP ($p = 0.002$). Patients without NP had a significant higher daytime frequency and an increased mean daytime voided volume compared to those with NP (daytime frequency: $p = 0.023$ and mean daytime voided volume $p = 0.012$). Concerning the nocturnal parameters, no differences amongst patients with and without NP, defined based of the RFP, could be withheld (Table 1).

Comparing the baseline and after treatment situation of the NP and the non-NP group, a significant lower fluid intake in both groups was observed after treatment (NP, $p = 0.021$ and no NP $p = 0.007$). Moreover, in women without NP at baseline, a lower daytime frequency was observed after treatment ($p = 0.025$). No impact of HT on other FVC parameters could be observed When comparing the after treatment situation between women with and without NP at baseline, no changes could be witnessed (Table 1).

3.2.2. Subjective bladder parameters

Equal observations were made when observing the questionnaires, as no significant change in voiding and frequency disorders was observed after 3 months of HT amongst the total group (Voiding disorder: $p = 0.8$ before: 1/12 (0/12–1.3/12), after: 0/12 (0/12–2.5/12)) and (Frequency disorder: $p = 0.2$, before: 2/16 (2/16–4/16), after: 3/16 (1/16–3/16)). However, a significant improvement in incontinence was noticed after HT ($p = 0.026$; before: 2/20 (1/20–4/20), after: 2/20 (0/20–2.5/20)) (Fig. 1).

In line with the total population, women with NP at baseline described a significant improvement of their incontinence problems after treatment ($p = 0.03$, before: 2/20 (1/20–4/20), after treatment: 2/20 (0.3/20–3/20)). This finding is in contrast to women without NP, who described an improvement of frequency problems ($p = 0.03$; before: 3/16 (1/16–4/16) and after 2/16 (1/16–3/16)). HT did not impact voiding disorders in either groups.

3.3. Renal parameters

3.3.1. Circadian rhythms at baseline

In patients without NP, a clear circadian rhythm amongst diuresis rate was observed as the diuresis rate significantly decreased during night-time compared to daytime ($p = 0.001$). A similar rhythm was observed for sodium clearance ($p = 0.005$). However, no significant circadian rhythm was observed for FWC in patients without NP at baseline ($p = 0.1$) (Table 2 and Fig. 2).

In patients presenting with NP at baseline, no circadian rhythm for diuresis rate and sodium clearance could be observed, as for both

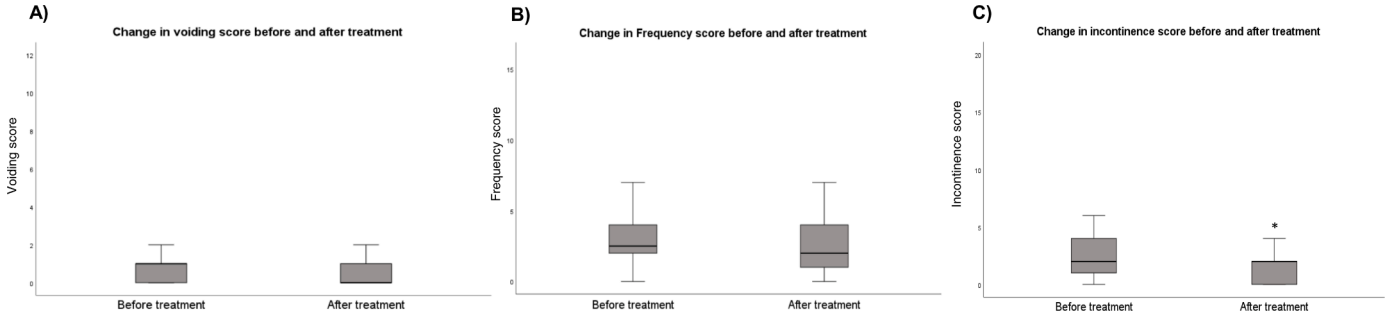

Fig. 1. Impact of 3 months of HT on voiding score, frequency score and incontinence score before and after treatment assessed using the ICIQ-FLUTS amongst the total group. A significant improvement is seen for incontinence score after treatment and is marked with a *. No significant improvement amongst frequency and voiding scores was seen.

Table 2
Overview of the day and night-time clearance of diuresis rate, sodium clearance and free water clearance at baseline and after 3 months of HT for the nocturnal polyuria (NP) group and non – NP group.

	No nocturnal polyuria $N = 15$						Nocturnal polyuria $N = 17$					
	At baseline			After treatment			At Baseline			After treatment		
	Day	Night	P-value*	Day	Night	P-value*	Day	Night	P-value*	Day	Night	P-value*
Diuresis rate (ml/min)	2.33 (1.81 – 2.58)	0.97 (0.66–1.64)	**0.001**	1.75 (1.28 –2.29)	1.46 (1.21–1.85)	0.3	1.33 (1.09–1.69)	1.57 (1.16–1.84)	0.4	1.2 (0.68–1.61)	1.3 (0.99–1.78)	0.2
Sodium Clearance (ml/min)	0.98 (0.83–1.24)	0.49 (0.33–0.73)	**0.005**	0.94 (0.66–1.18)	0.68 (0.36–1.01)	0.08	0.82 (0.77–1.29)	0.67 (0.60 - 1.05)	0.06	0.66 (0.45–0.83)	0.64 (0.51–0.80)	0.7
Free water clearance (ml/min)	−0.08 (−0.62–0.17)	−0.53 (- 0.77 - - 0.02)	0.1	−0.75 (- 1.23 - −0.45)	−0.32 (−0.84–0.13)	0.056	−0.95 (−1.40–- 0.51)	−0.23 (−0.66–0.45)	**0.011**	−0.6 (−1.11 - −0.31)	−0.54 (- 0.93 - −0.43)	**0.02**

* Comparisons were made using the Wilcoxon–signed–rank test. A p–value < 0.05 was considered significant and highlighted in bold.

parameters the daytime and night-time values did not significantly differ (diuresis rate: $p = 0.4$; sodium clearance: $p = 0.06$). However, an inverse circadian rhythm for FWC was observed, as the FWC during night-time was significantly higher than during daytime ($p = 0.01$) (Table 2 and Fig. 2).

Women defined as having NP at baseline had a significant lower diuresis rate during daytime compared to those without NP ($p = 0.001$) ml/s. The overnight diuresis was significantly higher amongst women with NP, reflecting the nocturnal overproduction ($p = 0.01$). As expected, the overnight sodium clearance was higher in patients with NP compared to those without ($p = 0.04$). Night-time FWC did not differ significantly between both groups ($p = 0.2$). However, daytime FWC was significantly increased in women with NP ($p < 0.001$).

3.3.2. *Circadian rhythms after treatment*

Three months of HT led to a disappearance of the circadian rhythm of diuresis rate and sodium clearance in patients without NP at baseline, as no significant difference between daytime and night-time values was observed (diuresis rate $p = 0.3$; sodium clearance $p = 0.08$). However, the treatment did not impact FWC, as equal to baseline values no significant difference between day and night values was observed ($p = 0.056$). In patients with NP, treatment did not induce a circadian rhythm for diuresis rate and sodium clearance ($p = 0.2$ and $p = 0.7$, respectively). By contrast, the rhythm of FWC did change to a mild circadian rhythm with a high FWC during daytime compared to night-time values ($p = 0.02$).

A significant difference in both daytime and total diuresis rate was observed between both groups (daytime: $p = 0.02$; total: $p = 0.04$. Moreover, a significant higher sodium clearance during daytime was observed in patients without NP ($p = 0.047$).

A clear overview of the observed impact of HT on both voiding difficulties and the circadian rhythms of urine production is given in Table 3.

4. Discussion

This study is the first to observe the impact of HT on the circadian rhythms of water and salt diuresis in postmenopausal women with and without NP. The results of this pilot trial suggest a negative impact of HT on the circadian rhythm of diuresis rate and salt clearance in patients without NP, an improvement of the circadian rhythm of FWC in those with NP and a global improvement on daytime frequency and a lower fluid intake after treatment.

In the current study, baseline RFP assessment observed clear circadian rhythms of diuresis rate and sodium clearance in patients without NP and a disabled rhythm in patients presenting with NP. These findings are similar to earlier research conducted in a large group of multi-aged patients with NP [4,19]. HT did not change the disrupted rhythm of diuresis rate and sodium clearance in patients with NP. On the contrary, patients without NP at baseline lost their initial rhythms of both sodium clearance and diuresis rate after HT. However, the initial disrupted circadian rhythm of FWC in patients with NP at baseline changed to a normal rhythm with a significantly lower night-time clearance compared to the daytime values after HT. Nevertheless, these changes were small, without impact on the rhythms of sodium clearance and diuresis rate and nocturnal fluid production. Our findings were opposite to those by Stachenfeld et al. [16], who found increased water retention after HT in postmenopausal women but attributed this finding rather to increased sodium reabsorption than through a higher concentration of ADH. In our pilot trial, it can be concluded that the kidney, and more precisely the water and salt diuresis driven through ADH release and RAAS stimulation was not clearly affected by HT.

A FVC is an ideal instrument to observe treatment effect on bladder capacity and frequency. Equal to the findings of Virtanen et al. [28], our study observed a lower fluid intake in women treated with HT. Possibly, this finding can be explained by the improving effect of HT on oral

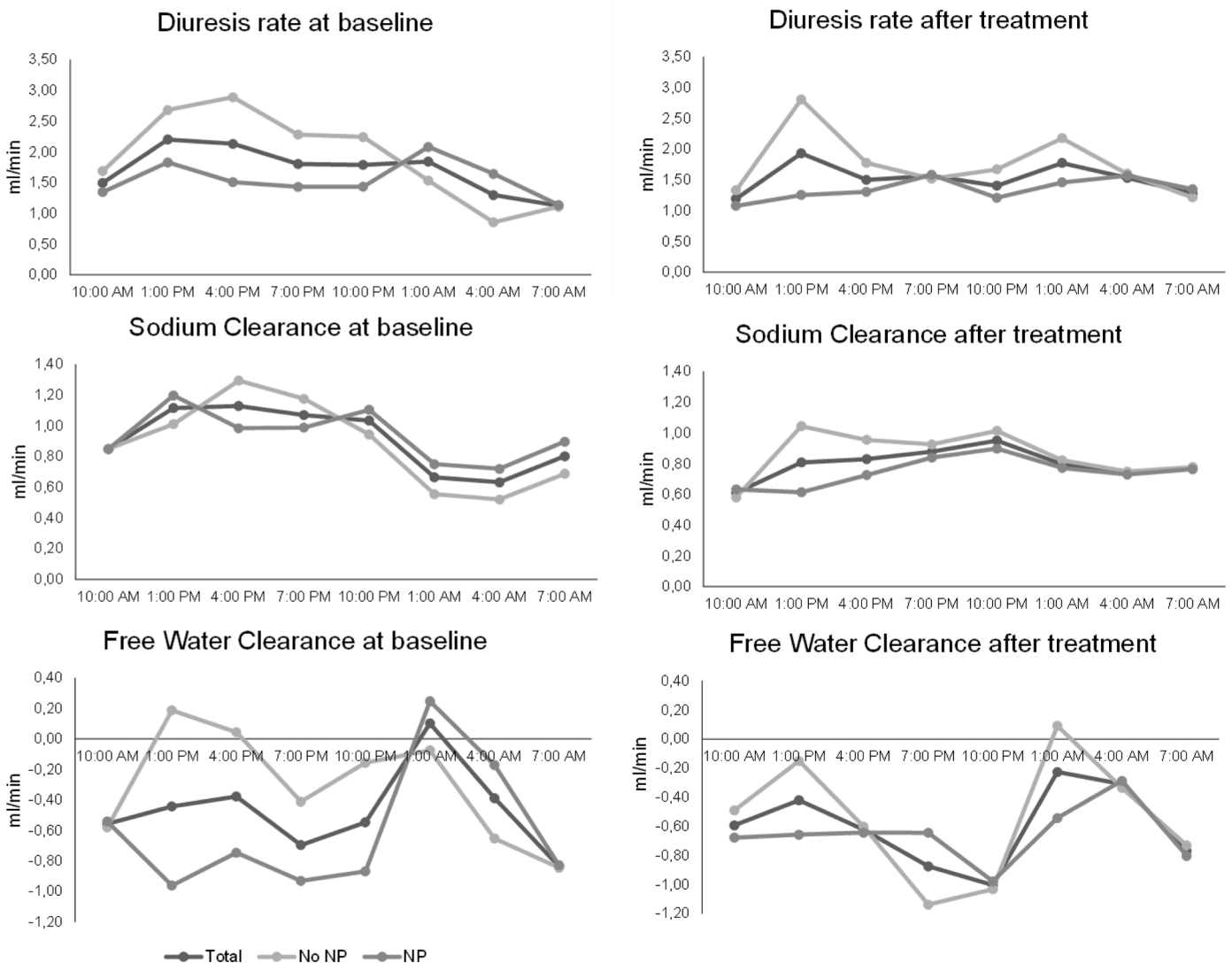

Fig. 2. The impact of 3 months of HT on the diuresis rate, sodium clearance and free water clearance of all women, women, women with NP and women without NP.

dryness through stimulation of the oestrogen receptors in the oral cavity [28]. This reduced fluid intake, which counts for a volume of approximately 200 ml, explains the significant reduction of daytime voiding frequency, as it corresponds with the volume of 1 toilet visit.

The findings of the questionnaires are in line with those collected from the FVC, as both showed no improvement of frequency and voiding symptoms. It must be noted that frequency and voiding symptoms at baseline were low and the burden due to these complaints was limited. Nevertheless, a significant improvement in incontinence symptoms was observed, which is in line with the findings of Cardozo et al. [29]. They observed in their meta-analysis a significant improvement of urinary incontinence in women treated with HT compared to placebo. Moreover, no effect of HT on frequency and urgency compared to women treated with placebo was observed [29]. For this pilot study, it can be concluded that HT did not affect the bladder function and storage capacities.

In the current trial, nocturnal frequency did not improve after HT. Earlier research observed a significant improvement of nocturnal frequency in patients treated with HT [24]. Moreover, Pauwaert et al. observed a significant decrease in nocturia prevalence (defined as ≥ 2 voids per night) but contributed the effect to a significant improvement in sleep quality and sleep disorders [30]. Probably, the sample size of our pilot study was too limited and the prevalence of nocturia was too low to observe clear effects.

This study is the first to observe the impact of HT on voiding patterns and water and salt diuresis in postmenopausal women with and without NP. The findings in this study are important as NP is the predominant underlying cause of nocturia. Based on the results of the current trial, it can be suggested that the improving effect of HT on nocturia that was demonstrated in earlier research [30], is most likely based on the improving effect of HT on postmenopausal sleep problems (hot flushes and insomnia), rather than the effect of HT on voiding dysfunctions and diuresis. However, as this study reports a reestablishment of the circadian rhythm of FWC in NP patients, this can be a possible explanation for the lower nocturnal frequency as well. Further research is necessary to confirm these findings.

Nevertheless, based on this current results, it can be hypothesised that HT can only treat nocturia in patients where the predominant origin of the nocturia is an underlying sleep disorder. Moreover, it can be hypothesised that HT does not treat nocturia which is provoked by NP or reduced bladder capacity. Presumably, this hypothesis can include a possibility for future personalized medicine, whereas depending on the underlying ethology of nocturia, patients may be better treated with systemic or vaginal HT. However, a large randomised trial including vaginal, transdermal and oral oestrogen is necessary to consolidate these findings.

Table 3
General overview of the impact of 3 months of HT on renal circadian rhythms and both objective and subjective bladder parameters. Green represents significant improvement of the parameter, red represents a significant adverse impact of HRT on the parameter and grey represent no significant change of HT on the parameter.

	Nocturnal polyuria N = 17	No nocturnal polyuria N = 15
Objective bladder parameters		
Fluid intake		
Total urine volume		
Night-time volume		
Daytime frequency		
Night-time frequency		
Subjective bladder parameters		
Voiding		
Frequency		
Incontinence		
Circadian rhythm of renal parameters		
Diuresis rate		
Sodium clearance		
Free water clearance		

This research had some limitations as it is a **pilot study with only one single-test group in a pre-post design, without parallel comparing with active treatment or a placebo control. Moreover, the power of the current study is limited and**a selection bias can be withhold as women were only recruited on the gynaecology department of a tertiary hospital. Secondly, the follow-up time of the study was rather limited. Subsequently, this study was not randomised and included no patients using vaginal estrogens. Moreover, no estimations of underlying sleeping disorders were made. Patient's food intake was not standardised so sodium intake can differ between participants. Lastly, an inherent limitation of FVC is the day- to-day variability of the observations. In this study, minimal differences were observed between data obtained using the FVC and the RFP, which indicates that volume intake and diuresis can vary significantly per day and per person. Further research should include an extended study, comparing the effect of different types of HRT on questionnaires, FWC and RFP's in order to make a distinct conclusion.

5. Conclusion

Three months of HT led to a significant reduce in fluid intake resulting in a lower daytime frequency in postmenopausal women. For women without NP at baseline, HT impacted the circadian rhythms of diuresis rate and sodium clearance negatively as a disruption of those rhythms was seen after treatment. In patients with NP, a minimal effect with a normalisation of the circadian rhythm of FWC was observed.

Contributors

Kim Pauwaert contributed to data management, statistical analysis, writing the original draft, and review and editing of the draft paper.

Elke Bruneel contributed to conceptualization, data management, and review and editing of the draft paper.

Erik Van Laecke contributed to review and editing of the draft paper.

Herman Depypere contributed to conceptualization, patient recruitment, and review and editing of the draft paper.

Karel Everaert contributed to conceptualization, and review and editing of the draft paper.

An-Sofie Goessaert contributed to writing the original draft, and review and editing of the draft paper.

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Ethical approval

This study was approved by the Ethical Committee of Ghent University Hospital (EC2014/1241). The Declaration of Helsinki was followed and conducted in accordance to the legal regulations in Belgium. Written informed consent was obtained from all participants included in the study.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

Declaration of competing interest

Dr. Kim Pauwaert receives a research grant from Ferring.

Prof. Dr. Karel Everaert reports grants and other from Ferring, grants from Astellas, grants and other from Medtronic, outside the submitted work; and is a minority shareholder and co-founder without salary or honoraria of P2Solutions (smart textile applications), which could be perceived to have influence but have not.

The other authors declare that they have no competing interests.

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