Decreased renal function increases the nighttime urine volume rate by carryover of salt excretion to the nighttime

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Research Article

Keywords: nocturia, nocturnal polyuria, kidney disease, renal dysfunction

Posted Date: March 3rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-251676/v1

Abstract

Purpose: To determine the pathophysiology of nocturnal polyuria associated with renal dysfunction.

Methods: Patients who underwent laparoscopic nephrectomy were studied prospectively. The diurnal variation in urine volume, osmolality, and salt excretion were measured on preoperative day two and postoperative day seven. The factors associated with an increase in the nighttime urine volume rate with decreased renal function were evaluated by multiple linear regression analysis.

Results: Forty-nine patients were included. The eGFR decreased from 73.3 ± 2.0 to 47.2 ± 1.6 mL/min/1.73 m^2 ($P < 0.01$) and the nighttime urine volume rate increased from 40.6% ± 2.0% to 45.3% ± 1.5% ($P = 0.04$) with nephrectomy. The nighttime urine osmolality decreased from 273 ± 15 to 212 ± 10 mOsm/kg ($P < 0.01$) and the nighttime salt excretion rate increased from 38.7% ± 2.1% to 48.8% ± 1.7% ($P < 0.01$) with nephrectomy. Multiple linear regression analysis revealed that the increase in the nighttime urine volume rate was strongly affected by the increase in the nighttime salt excretion rate.

Conclusion: A decrease in renal function causes an increase in the nighttime urine volume rate, mainly due to an increase in nighttime salt excretion.

Trial registration number: UMIN000036760 (University Hospital Medical Information Network Clinical Trials Registry)

Date of registration: From June 1st, 2019 to October 31th 2020

Introduction

Nocturnal polyuria, which is defined as “excessive production of urine during the individual’s main sleep period” [1], is considered to be caused by various medical conditions. Nocturnal polyuria is the most common cause of nocturia, accounting for 67–88% of all nocturia cases [2, 3]. Nocturia is defined as “the number of times an individual passes urine during their main sleep period” [1]. Nocturia is a common lower urinary tract symptom in older people, and its incidence is estimated to be > 60% in older people aged > 65 years [4]. Nocturia is not only a troublesome symptom that affects quality of life [5], but has also recently been shown to be a risk factor for depression and death [6, 7]. Therefore, treating nocturia may improve the quality of life in older people and reduce the risk of depression and death. However, the pathogenesis of nocturnal polyuria is complex and not well understood, and no fundamental treatment has been established. This is because research is scarce on clarification of the mechanism of nocturnal polyuria. Many epidemiological studies have reported involvement of various diseases and lifestyles in nocturnal polyuria, but most studies were cross-sectional and did not accurately determine the influence of each factor [8]. To establish a treatment for nocturia, the pathogenesis of nocturnal polyuria needs to be clarified.

Because many patients with chronic kidney disease (CKD) present with nocturnal polyuria, renal dysfunction is considered to be one of the causes of nocturnal polyuria. A CKD-induced deficit in urinary concentration and increased salt excretion may be the mechanism that leads to nocturnal polyuria [9]. However, no studies have proved a causal relationship between renal dysfunction and nocturnal polyuria or determined its mechanism, and the exact causal relationship and mechanism are not well understood. Therefore, in this study, we aimed to examine the mechanism of nocturnal polyuria in renal dysfunction by prospectively investigating the changes in daytime and nighttime urine volume and urine salt excretion before and after nephrectomy in the same individuals. Identification of the mechanism of nocturnal polyuria is expected to lead to establishment of a treatment strategy for nocturnal polyuria and nocturia.

Material And Method

Study participants and study design

We included patients who underwent laparoscopic nephrectomy at Osaka University Hospital from June 2019 to October 2020 in this study. Blood and urine collection tests were prospectively performed two days before and seven days after nephrectomy to investigate the changes in renal function and daytime and nighttime urine volume, urine osmolality, and salt excretion. The laparoscopic nephrectomy was performed by retroperitoneal approach and all surgical manipulations were performed extraperitoneally. The day after surgery, the intravenous fluid was discontinued and oral food intake was started. Patients with hydronephrosis preoperatively, patients on hemodialysis, and patients with diabetes and positive urine glucose were excluded.

Evaluation Of Renal Function

Renal function was assessed by the estimated glomerular filtration rate (eGFR). The eGFR was calculated from serum creatinine (sCr) levels in early morning fasting blood samples using the following equation: eGFR (mL/min/1.73 m^2) = $194 \cdot sCr^{-1.094} \cdot age^{-0.287} \cdot 0.739$ (if female) [10].

Evaluation Of Urinary Parameters

Twelve-hour urine collection tests were performed, and urine from 10:00–22:00 h was defined as daytime urine, and urine from 22:00–10:00 h as nighttime urine. Urinary sodium (U_{Na}), potassium (U_K), urea nitrogen (U_{UN}), and creatinine (U_{Cr}) were measured in each period. The nighttime urine volume rate was defined as nighttime urine volume/daily urine volume. Urine osmolality was calculated using the following formula: urine osmolality (mOsm/kg) = $2 \cdot (U_{Na} + U_K) + U_{UN}/2.8$. The nighttime salt excretion rate was defined as nighttime salt excretion/daily salt excretion. Fractional excretion of sodium (FE_{Na}) was calculated using the following formula: FE_{Na} (%) = $(U_{Na}/\text{serum Na})/(U_{Cr}/sCr) \cdot 100$.

Statistical analysis

Results are expressed as the mean ± SEM or median with interquartile range (IQR). The significance of differences between preoperative and postoperative data was tested by the paired *t*-test. Multiple linear

regression analysis was performed to identify independent variables to determine the increase in the nighttime urine volume rate, with the preoperative nighttime urine volume rate as a covariate. The significance of difference between the change in rate of eGFR (decrease) and daytime FE_{Na} was tested by the Wilcoxon signed rank test. A *P* value < 0.05 was considered statistically significant. All statistical tests were performed using JMP 14 (SAS Institute, Cary, NC).

Results

Participants' characteristics

There were 49 participants in this study. The characteristics of participants are shown in Table 1.

Table 1. Characteristics of the subjects (n = 49)

Median Age, years (Range)	64	(39–89)
No. Male (%)	24	(49)
No. Reasons for nephrectomy (%)		
Kidney transplant donor	36	(73)
Renal cancer	11	(22)
Renal pelvis cancer	2	(4)
Median Operative time, min (Range)	210	(123–374)
Median Blood loss, mL (Range)	20	(0–140)
No. Comorbidities (%)		
Hypertension	17	(35)
Dyslipidemia	6	(12)
Diabetes mellitus	3	(6)
Cerebrovascular disease	2	(4)
Malignant tumors	2	(4)

Changes In The EGFR

The eGFR was significantly decreased after nephrectomy (47.2 ± 1.6 mL/min/1.73 m^2) compared with before nephrectomy (73.3 ± 2.0 mL/min/1.73 m^2, *P* < 0.01) (Fig. 1A).

Changes In Daytime And Nighttime Urine Volume

Nephrectomy significantly increased daytime urine volume (from 1214 ± 79 to 1431 ± 84 mL, $P = 0.01$) and nighttime urine volume (from 820 ± 57 to 1155 ± 62 mL, $P < 0.01$) (Fig. 1B, C), and increased the nighttime urine volume rate (from 40.6% ± 2.0–45.3% ± 1.5%, $P = 0.04$) compared with before nephrectomy (Fig. 1D). These findings indicate that decreased renal function increases the nighttime urine volume rate.

Changes in daytime and nighttime urine osmolality and salt excretion

Nephrectomy significantly decreased daytime urine osmolality (from 300 ± 22 to 195 ± 12 mOsm/kg, $P < 0.01$) and nighttime urine osmolality (from 273 ± 15 to 212 ± 10 mOsm/kg, $P < 0.01$) compared with before nephrectomy (Fig. 1E, F). However, nephrectomy decreased daytime salt excretion (from 4.33 ± 0.29 to 3.36 ± 0.20 g, $P < 0.01$), increased nighttime salt excretion (from 2.74 ± 0.21 to 3.20 ± 0.17 g, $P = 0.04$), and increased the nighttime salt excretion rate (from 38.7% ± 2.1–48.8% ± 1.7%, $P < 0.01$) compared with before nephrectomy (Fig. 1G–I). These findings indicate that decreased renal function causes carryover of salt excretion to the nighttime.

Factors associated with the increase in nighttime urine volume rate in renal dysfunction

The results mentioned above indicate that impaired renal function decreases urine osmolality and increases nighttime salt excretion. Both of these changes could affect the nighttime urine volume rate. To identify the factors associated with an increased nighttime urine volume rate with impaired renal function, we conducted multiple linear regression analysis. This analysis showed that age, a change in nighttime urine osmolality, the preoperative nighttime salt excretion rate, and a change in the nighttime salt excretion rate were significantly associated with the nighttime urine volume rate (all $P < 0.01$). Of these factors, a change in the nighttime salt excretion rate had the highest standard partial regression coefficient and had the strongest effect on the nighttime urine volume rate (Table 2).

Table 2. Factors associated with the increase in nighttime urine volume rate

Variables	Simple Linear Regression			Multiple Linear Regression			
	coefficient	(95% CI)	*P*	Unstandardized coefficient	(95% CI)	Standardized coefficient	*P*
Age	0.10	(-0.27, 0.48)	0.59	0.26	(0.10, 0.42)	0.20	< 0.01
Pre eGFR	-0.01	(-0.35, 0.32)	0.94				
Pre Nighttime Urine Osmolality	0.01	(-0.04, 0.05)	0.68				
Pre Nighttime Salt Excretion Rate	-0.68	(-0.94, -0.43)	< 0.01	-0.64	(-0.84, -0.44)	-0.57	< 0.01
ΔeGFR	-0.13	(-0.82, 0.55)	0.70				
ΔNighttime Urine Osmolality	-0.02	(-0.07, 0.02)	0.35	0.03	(0.01, 0.05)	0.17	< 0.01
ΔNighttime Salt Excretion Rate	0.73	(0.55, 0.91)	< 0.01	0.62	(0.47, 0.78)	0.65	< 0.01

Pre, Preoperative; eGFR, estimated glomerular filtration rate

Changes In Daytime And Nighttime FE

To investigate the causes of the increase in the nighttime salt excretion rate (i.e., carryover of salt excretion to the nighttime after nephrectomy) we compared changes in the eGFR and FE_{Na} with nephrectomy. Nephrectomy increased daytime FE_{Na} (from 0.83% ± 0.04–1.03% ± 0.05%, $P < 0.01$) and nighttime FE_{Na} (from 0.66% ± 0.05–1.07% ± 0.06%, $P < 0.01$) compared with before nephrectomy (Fig. 1J, K). The rate of change (increase) in daytime FE_{Na} (16.7%; IQR, − 5.8 to 47.3) was significantly lower than the rate of change (decrease) in the eGFR (35.9%; IQR, 31.48 to 41.05, $P = 0.03$) (Fig. 1L).

Discussion

In this study, we prospectively investigated the changes in urine volume, urine osmolality, and salt excretion during the daytime and nighttime before and after nephrectomy. We found that the nighttime urine volume rate increased as renal function decreased. Additionally, the increase in the nighttime urine volume rate with decreased renal function was strongly related to the increase in nighttime salt excretion. Furthermore, we found that the rate of change (increase) in daytime FE_{Na} was significantly lower than the rate of change (decrease) in the eGFR. This insufficient increase in daytime FE_{Na} compared with a

decrease in the eGFR may be the cause of the decrease in daytime salt excretion. This finding suggests that renal dysfunction decreases daytime salt excretion, which results in increased salt excretion at nighttime. Our findings suggest that the main cause of the increase in the nighttime urine volume rate in renal dysfunction is carryover of salt excretion to the nighttime.

The reason why FE_{Na} did not increase as the eGFR decreased in our study is unclear. If the rate of increase in FE_{Na} and the rate of decrease in the eGFR were comparable, salt excretion during the daytime would not decrease, and the nighttime urine volume rate would not be increased as much. Although we do not know the exact mechanism of our finding, there might not be a system present in the human body for rapid excretion of excess salt intake. In the process of evolution, humans have developed a urine reabsorption system in the kidney, including the glomerulus, tubule, and Henle's loop, and have the ability to reabsorb more than 99% of Na [11]. People can survive on a small amount of salt, as shown by the Yanomamo who survive on a salt intake of < 1 g/day [12]. However, most people consume approximately 10 g of salt a day, which is believed to be too high. Various diseases in the current era, such as hypertension and stroke, are related to excessive salt intake [13]. Humans have only really been consuming this high amount of salt for approximately 5,000–10,000 years [14], and have therefore not yet acquired the ability to rapidly excrete excess salt.

Recently, nocturia, which is a common lower urinary tract symptom in older people, has been found to be not only a cause of decreased quality of life, but also a risk factor for depression and death [6, 7]. The causes of nocturia include global polyuria, nocturnal polyuria, bladder storage problems, and sleep disorders [15], of which the most common cause is nocturnal polyuria [2]. Nocturnal polyuria may be a multifactorial condition with many possible contributing factors, including behavioral, physiological, and pathological factors. Renal dysfunction is considered to be one of the causes of nocturnal polyuria, because nocturnal polyuria is one of the initial symptoms in patients with CKD. A decrease in urine concentrations and an increase in nocturnal salt excretion may be a cause of nocturnal polyuria in decreased renal function [9]. However, previous studies on this issue were cross-sectional and had limited ability to prove causality. In the present study, we performed prospective analysis of changes in urine volume, urine osmolality, and salt excretion during the daytime and nighttime before and after nephrectomy. We found that the increase in nocturnal urine volume associated with renal dysfunction was due to carryover of salt excretion to the nighttime.

Excessive salt intake has attracted attention as one of the causes of nocturnal polyuria [16, 17]; However, there are also negative reports on the relationship between nocturnal polyuria and excessive salt intake [18, 19]. Therefore, whether excessive salt intake is a cause of nocturnal polyuria remains controversial. In this study, we investigated the effect of decreased renal function on nocturnal polyuria, and found that salt excretion was carried over to the nighttime and the nocturnal urine volume rate increased when renal function decreased. This suggests that renal dysfunction is involved in the association between excessive salt intake and nocturnal polyuria. Therefore, when people with impaired renal function consume excessive salt, salt excretion may be carried over to the nighttime, resulting in nocturnal polyuria. In cases of nocturia due to this mechanism, a reduction in salt intake or administration of

diuretics, such as thiazide, may be useful in reducing nocturnal salt excretion and nocturnal urine. However, the criteria for excessive salt intake in terms of nocturnal polyuria are unknown, and future research is required to establish the criteria of optimal salt intake.

There is a limitation of this study. This was a one-arm study and we did not have controls. Therefore, we were not able to accurately assess the effect of decreased renal function. The surgical stress may cause a variety of stress responses to the patient, which may affect the urine production and salt excretion. For example, cortisol, which is one of the stress hormone, is known to cause retention of sodium and may affect salt excretion. A study of patients undergoing non-nephrectomy surgery as controls would have allowed us to accurately assess the effect of decreased renal function on nocturnal polyuria. However, in this study, the level of surgical stress is considered to be moderate, because all surgeries were performed laparoscopically and extraperitoneally, with shorter operative time, less blood loss, and less intravenous fluid infusion. In fact, a previous study showed that, in patients who underwent laparoscopic nephrectomy, blood cortisol levels increased immediately after surgery, but returned to preoperative levels one day after surgery [20]. Therefore, we believe that the effect of the stress response on the conclusion of this study may be limited.

Conclusions

The present study shows that a decrease in renal function causes a decrease in nighttime urine osmolality, a decrease in daytime salt excretion, and an increase in nighttime salt excretion. Among these factors, the increase in the nighttime salt excretion rate was found to have the strongest effect on the increase in the nighttime urine volume rate. These results suggest that decreased renal function increases the nighttime urine volume rate via carryover of salt excretion to the nighttime.

Declarations

Authors' contributions:

K Takezawa: Project development, Data collection, Manuscript writing

S Kuribayashi: Data collection

K Okada: Data collection

Y Sekii: Data collection

Y Inagaki: Data collection

S Fukuhara: Data collection

K Hiroshi: Project development, Data collection, Manuscript writing

A Toyofumi: Data collection

K Fujita: Data collection

M Uemura: Data collection

R Imamura: Data collection

N Nonomura: Project development

Declarations:

Funding:

The authors did not receive support from any organization for the submitted work.

Availability of data and material:

None

Code availability:

Not applicable

Compliance with Ethical Standards:

1. Disclosure of potential conflicts of interest:

The authors have no conflicts of interest to declare that are relevant to the content of this article.

2. Research involving Human Participants and/or Animals:

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Osaka University Graduate School of Medicine (No. 18418).

3. Informed consent:

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: Informed consent was obtained from all individual participants for whom identifying information is included in this article.

Acknowledgments:

We thank Ellen Knapp, PhD, from Edanz Group (https://en-author-services.edanz.com/ac) for editing a draft of this manuscript.

Conflicts of interest:

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Figures

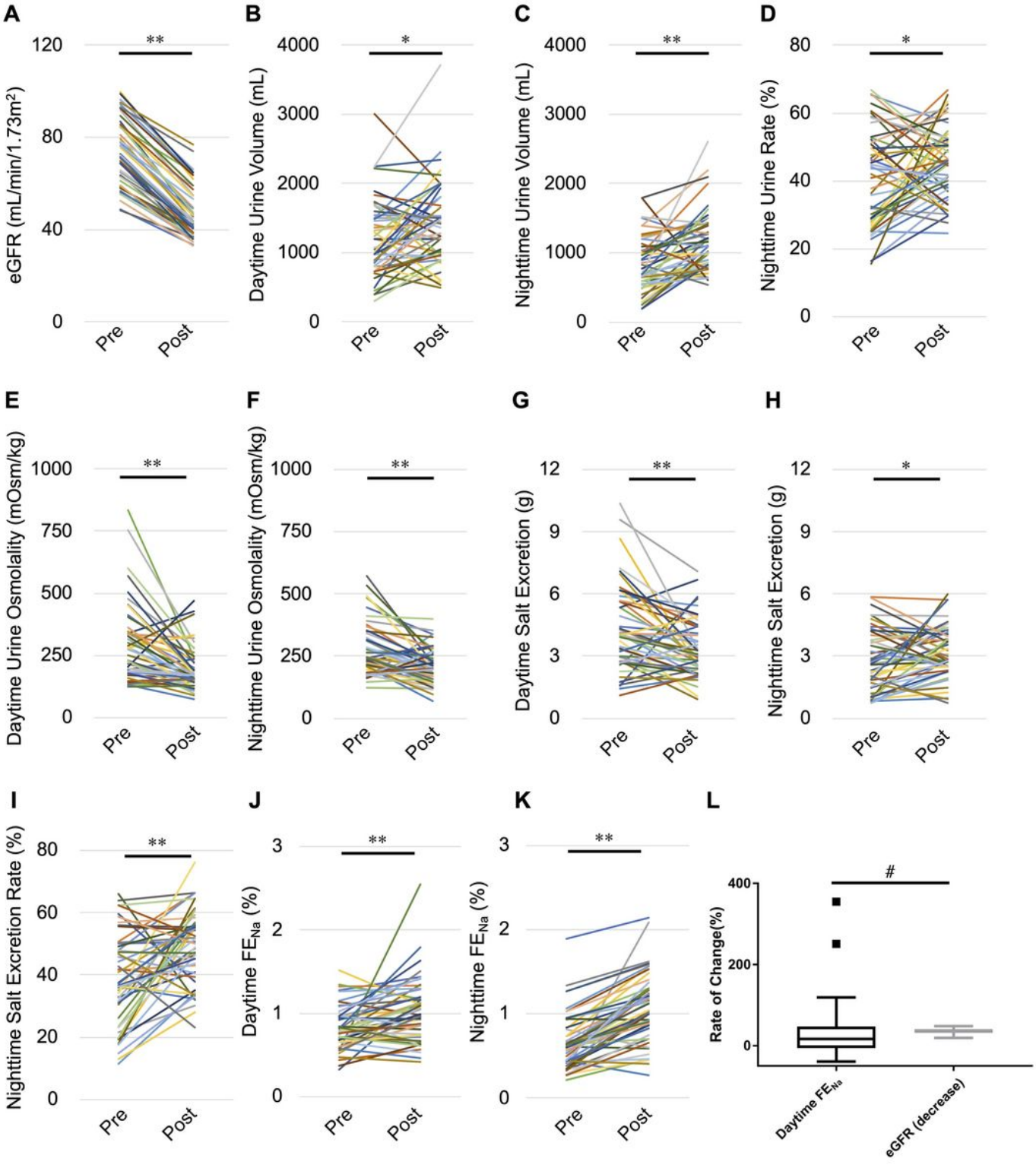

Figure 1

Changes in (A) eGFR, (B) daytime urine volume, (C) nighttime urine volume, (D) nighttime urine volume rate, (E) daytime urine osmolality, (F) nighttime urine osmolality, (G) daytime salt excretion, (H) nighttime salt excretion, (I) the nighttime salt excretion rate, (J) daytime FENa and (K) nighttime FENain each patient, and (L) Tukey's box and whisker plots for rate of changes in daytime FENa and the eGFR (decrease) eGFR, estimated glomerular filtration rate; Pre, preoperative; Post, postoperative; FENa,

fractional excretion of sodium. *P < 0.05, **P < 0.01, by the paired t-test; #P < 0.05, by the Wilcoxon signed rank test.

Supplementary Files

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- Table1.xlsx
- Table2.xlsx