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Effect of salt intake reduction on nocturia in patients with excessive salt intake

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Aims: To assess the efficacy of salt reduction for improving nocturia in patients with high salt intake.

Methods: Changes in lower urinary symptoms and frequency volume chart by salt intake (men: 8 g/day; women: ≥7 g/day) were analyzed in this prospective study. Patients were instructed to use a brochure for salt intake restriction via interview once every four weeks. The daily salt intake was estimated by using spot urine samples.

Results: Two-hundred twenty-three (69.5%) patients were successful in reducing their daily salt intake (S group), whereas 98 (30.5%) patients failed to reduce their salt intake (F group). In the S group, nocturia improved from 2.3 ± 0.9 to 1.4 ± 1.0, and nocturnal polyuria index (NPi) improved from 30.2 ± 7.5 to $27.7 \pm 7.3\%$ ($P < 0.001$). In the Core Lower Urinary Tract Symptom Score (CLSS) of the S group, Q3 (urgency) improved from 1.0 ± 1.0 to 0.9 ± 1.0 ($P = 0.001$); Q1 (diurnal frequency) ($P < 0.001$), and Q2 (nocturia) also improved ($P < 0.001$). Moreover, the quality of life parameter improved significantly ($P < 0.001$). The patients in the F group did not have improvements in any symptom during the study period.

Conclusions: Patients with nocturia who also have high salt intake should be advised to reduce their salt intake, as a lifestyle modification. Our results support the importance of randomized clinical trials with larger populations and the appropriate inclusion/exclusion criteria to conclude the clinical usefulness of salt reduction in this patient cohort.

KEYWORDS
lower urinary tract symptoms, nocturia, salt intake reduction, treatment

1 | INTRODUCTION

The lower urinary tract symptom (LUTS) is a common pathological condition, especially in the elderly, and it is related to a decrease in the quality of life (QOL). Pharmacotherapy is the major treatment for patients with LUTS, including nocturia. However, we must note that some drugs for LUTS have adverse events, which may sometimes worsen the QOL. For example, anticholinergic drugs that are used for the treatment of overactive bladder and the reduction of bladder capacity at nighttime are associated with an increased risks of cognitive impairment, constipation, dry mouth, voiding dysfunction, and cardiovascular disease.[1–3] In addition, elderly patients often take a variety of drugs for

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Ethics: This study was approved by the Nagasaki University Hospital Ethical Committee.

systemic diseases, and polypharmacy can further increase the risk of adverse events.[4] Moreover, in Japan, antidiuretic hormone, which causes nocturia secondary to nocturnal polyuria, is not approved for use against nocturia at present. Therefore, we emphasize the importance of non-pharmacological treatments for LUTS, including nocturia.

Previous reports have shown that programs of lifestyle modification, including eating habits, are useful interventions for LUTS.[5] In addition, weight loss[6] and water intake reduction[7] are reported to be effective in patients with overactive bladder or nocturia. However, the information on the efficacy of lifestyle modification for LUTS is insufficient, leading to problems when discussing this new treatment strategy in these patients. On the other hand, LUTS, including nocturia, is influenced by metabolic syndrome (Mets) and lifestyle-related diseases, such as hypertension, cardiovascular disease, diabetes mellitus, and renal dysfunction.[8–11] In addtion, excessive salt intake is reported to be one of the most crucial determinants for Mets and lifestyle-related diseases.[12,13] Although excessive salt intake may affect the occurrence of nocturia, there is no general agreement on the relationship between salt intake and nocturia.[14–16]

Unfortunately, these studies have a cross-sectional design, and there is a need for prospective studies to clarify the clinical roles of salt intake. In this prospective study, we aimed to investigate whether reduced salt intake can affect LUTS, including nocturia and to determine whether salt intake reduction could be a new treatment option for these patients.

2 | PATIENTS AND METHODS

2.1 | Patients and nutrition guidance for salt intake

This prospective clinical study was carried out from September 2014 to March 2015 and included patients who woke up ≥1 time at night to void, who were bothered by nocturia, and who were identified as having excessive salt intake (8 g/day or more for men; 7 g/day for women) in our hospital. The exclusion criteria were acute urinary tract infection and any condition affecting urinary function, including a history of pelvic surgery, obvious detrusor overactivity previously diagnosed by a urodynamic study, benign prostatic hyperplasia, urethral stricture, pelvic organ prolapse, urological malignancy, or neurogenic bladder. Patients administered with medications that could possibly affect sodium excretion (e.g., diuretic, antidiuretic hormone, and so on) were also excluded. We enrolled patients with nocturia and they were divided into two groups based on the success (S group) or failure (F group) of salt intake reduction.

Patients were provided with a brochure that served as a nutritional guide for salt intake restriction and received health education from physicians and nurses every four weeks. The brochure details the approximate salt intake contained in the common diet, and salt used as seasoning was described in detail.

This study was carried out in accordance with the principles of the Declaration of Helsinki and was approved by the ethical committee of our institution. All participants provided written informed consent.

2.2 | Evaluation of vital signs and urinary parameters

We defined hypertension as a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg, or receiving therapy for hypertension. Body height (cm) and weight (kg) measures were recorded and used to calculate body mass index (BMI) using the standard formula (BMI = weight [kg]/height [m]^2). Diurnal urine volume was defined as total urine volume voided after the first morning void to the last void before bed. Nocturnal urine volume (NUV) was defined based on the International Continence Society (ICS) standardization: total volume of urine passed during the night including the first morning void. Nocturnal polyuria index (NPi) was defined as the ratio of nocturnal and 24-h total urine production. Sodium concentration in the spot urine test was represented as Na concentration in the spot voiding urine (SUNa). Renal dysfunction was defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2. In addition, patients with end-stage renal disease (estimated glomerular filtration rate <15 mL/min/1.73 m^2) were excluded from the study.

2.3 | Evaluation of daily salt intake

We evaluated the various urological parameters before and 12 weeks after salt intake reduction. We assessed the changes in LUTS using the Core Lower Urinary Tract Symptom Score (CLSS)[17] and estimated salt intake volume by estimated urinary sodium excretion using spot urine samples. In addition, we asked the participants to complete the 3-day frequency volume charts (FVCs), and we evaluated the average urinary volume and frequency of the 3-day data. We used the spot morning (from 9:00 am to 11:00 am) urine samples, with one sample per one participant once a day, which the participants voided when they visited our institution to estimate the daily salt intake volume. According to a previous report, daily salt intake was used to estimate the sodium and creatinine concentrations in spot urine samples using the formula mentioned below, which was adjusted for body height and weight and age, and it seemed to have less impact on sample collection time and has a relatively high accuracy[18]: (24-h Na excretion [mEq/day] = 21.98 [Na S/(Cr S × 10) × Pr.UCr24]$^{0.392}$, Na S: Na concentration in spot urine [mEq/L], Cr S: Cr concentration in spot urine [mg/dL], Pr.UCr24:

Predicted 24 h urinary Cr excretion [mg/day] = −2.04 × age [years] + 14.89 × bodyweight [kg] + 16.14 × height [cm] − 2244.45].

2.4 | Statistical analysis

All data are expressed as mean ± SD, and values are described as mean ± SD. Student's *t*-test was used to compare parametric continuous variables. All statistical tests were performed using JMP 13 (SAS Institute, Cary, NC). Ohta et al previously reported the salt restriction success rate of 10.3% by using the nutrition guidance.[19] We set a probability of 0.05 (two-sided), a power of 80%, and an effect size of 0.5. We estimated that the ideal number of participants for this study should be at least 256.

3 | RESULTS

3.1 | Patients' characteristics

As summarized in Table 1, there were 321 participants (102 men and 219 women). The mean age was 64.3 ± 13.6 years, the mean BMI was 22.7 ± 3.8 kg/m^2, and the mean estimated salt intake was 10.3 ± 2.1 g/day. All participants were able to complete this study. When comparing the S ($n = 223$) and F ($N = 98$) groups, the BMI of the F group (23.4 ± 3.6 kg/m^2) was significantly higher than that of the S group (22.4 ± 3.9 kg/m^2) at baseline ($P = 0.017$). In addition, the proportion of the patients with hypertension and with renal dysfunction were significantly higher in the F group (hypertension: 63.3%; renal dysfunction: 44.9%) than in the S group (hypertension: 48.0%; renal dysfunction: 30.9%) (hypertension: $P = 0.011$; renal dysfunction: $P = 0.022$). Conversely, the estimated salt intake volume of the S group (10.7 ± 2.3 g/day) was significantly higher than that of the F group (9.6 ± 1.3 g/day) ($P < 0.001$) before the intervention. In addition, Table 2 shows the differences of the subjective and objective symptoms between the two groups at baseline. There were no significant differences between the two groups in the urological parameters using 3-day FVC. We did not find any statistical differences in the subjective symptoms using CLSS, except for the QOL score.

3.2 | Changes in estimated daily salt intake and FVC

Table 3 shows the changes in estimated daily salt intake and urological parameters using 3-day FVC. The patients in the S group had reduced daily salt intake volume from 10.7 ± 2.3 g/day to 8.0 ± 2.1 g/day ($P < 0.001$). Conversely, the patients in the F group had increased daily salt intake volume from 9.6 ± 1.3 g/day to 11.0 ± 1.8 g/day ($P < 0.001$). In the S group, the numbers of daytime and nighttime frequencies using 3-day FVC improved after nutritional guidance (daytime frequency: from 7.7 ± 2.4 to 6.4 ± 2.0, $P < 0.001$; nighttime frequency: from 2.3 ± 0.9 to 1.4 ± 1.0, $P < 0.001$). On the other hand, in the F group, the numbers of daytime and nighttime frequencies deteriorated after nutritional guidance (daytime frequency: from 7.6 ± 2.5 to 8.4 ± 2.6, $P < 0.001$; nighttime frequency: from 2.3 ± 1.1 to 2.7 ± 1.1, $P < 0.001$).

The fluid intake volume in the S group decreased from 2287.5 ± 577.1 mL/day to 1982.4 ± 524.3 mL/day ($P < 0.001$), whereas that in the F group increased significantly from 2262.2 ± 589.2 mL/day to 2540.3 ± 604.9 mL/day after 12 weeks ($P < 0.001$). The voided volume in the S group increased from 244.4 ± 24.5 mL to 255.8 ± 30.8 mL ($P < 0.001$), whereas that in the F group decreased significantly (from 241.9 ± 24.7 ml to 238.7 ± 23.9 ml, $P < 0.001$). Although the diurnal urine volume, NUV, and nocturnal NPi in the S group decreased significantly after nutritional guidance, those in the F group did not have statistically significant improvements in their symptoms (Table 3).

TABLE 1 Patients' characteristics before salt intake reduction in each group

	Entire ($n = 321$)	S group ($n = 223$)	F group ($n = 98$)	*P*-value
Sex Male/Female	102/219	67/156	35/63	0.315
Age (years)	64.3 ± 13.6	64.1 ± 13.8	64.8 ± 13.1	0.796
Body mass index (kg/m^2)	22.7 ± 3.8	22.4 ± 3.9	23.4 ± 3.6	0.017
Hypertension (%)	169 (52.6)	107 (48.0)	62 (63.3)	0.011
Diabetes mellitus (%)	39 (12.1)	27 (12.1)	12 (12.2)	0.972
Renal dysfunction (%)	113 (35.2)	69 (30.9)	44 (44.9)	0.022
Hyperlipidemia (%)	44 (13.7)	30 (13.5)	14 (14.3)	0.842
Fluid intake volume (ml/day)	2279.8 ± 580.0	2287.5 ± 577.1	2262.2 ± 589.2	0.733
*SUNa (mEq/L)	113.4 ± 50.4	115.4 ± 50.9	108.7 ± 49.0	0.436
Estimated 24-hr Urinary Na excretion (mEq/day)	176.2 ± 36.2	181.9 ± 39.3	163.2 ± 23.2	<0.001
Estimated daily salt intake (g/day)	10.3 ± 2.1	10.7 ± 2.3	9.6 ± 1.3	<0.001

*Na concentration in the spot urine.

TABLE 2 The differences of baseline's subjective and objective symptoms between two groups

	Entire ($n = 321$)	S group ($n = 223$)	F group ($n = 98$)	*P*-value
Daytime frequency	7.6 ± 2.4	7.7 ± 2.4	7.6 ± 2.5	0.842
Nighttime frequency	2.3 ± 1.0	2.3 ± 0.9	2.3 ± 1.1	0.898
1 (%)	52 (16.2)	37 (11.5)	15 (15.3)	0.517
2 (%)	176 (54.8)	117 (52.5)	59 (60.2)	
3 (%)	60 (18.7)	46 (20.6)	14 (14.3)	
>4 (%)	33 (10.3)	23 (10.3)	10 (10.2)	
Fluid intake volume (mL/day)	2279.8 ± 580.0	2287.5 ± 577.1	2262.2 ± 589.2	0.720
Voided volume (mL)	243.6 ± 24.6	244.4 ± 24.5	241.9 ± 24.7	0.397
Diurnal urine volume (mL)	1666.4 ± 492.5	1679.7 ± 492.0	1636.1 ± 494.9	0.466
Nocturnal urine volume (mL)	703.0 ± 198.9	702.0 ± 185.4	705.1 ± 227.5	0.898
Nocturnal polyuria index (%)	30.4 ± 7.8	30.2 ± 7.5	30.8 ± 8.3	0.543
CLSS				
Q1. Diurnal frequency	0.9 ± 0.9	0.8 ± 0.9	0.9 ± 1.0	0.978
Q2. Nocturia	1.9 ± 0.6	1.9 ± 0.6	1.9 ± 0.6	0.948
Q3. Urgency	1.0 ± 1.0	1.0 ± 1.0	1.0 ± 0.9	0.992
Q4. Urgency incontinence	0.7 ± 0.9	0.7 ± 0.9	0.6 ± 0.8	0.442
Q5. Stress incontinence	0.6 ± 0.9	0.6 ± 0.9	0.5 ± 0.8	0.177
Q6. Slow stream	1.3 ± 1.1	1.3 ± 1.1	1.3 ± 1.1	0.582
Q7. Strain	1.0 ± 1.1	1.0 ± 1.2	0.9 ± 1.1	0.906
Q8. Incomplete emptying	0.9 ± 1.1	0.9 ± 1.1	0.8 ± 1.0	0.303
Q9. Bladder pain	0.3 ± 0.7	0.3 ± 0.7	0.3 ± 0.6	0.835
Q10. Urethral pain	0.2 ± 0.6	0.2 ± 0.6	0.2 ± 0.5	0.973
QoL index	3.5 ± 1.2	3.6 ± 1.2	3.2 ± 1.2	0.009

S, success; F, failure; QoL, quality of life; CLSS, Core Lower Urinary Tract Symptom Score.

3.3 | Changes in CLSS score

Table 4 shows the changes in the CLSS between before and after the nutrition guidance in each group. The S group, which succeeded in salt intake restriction, showed improvement in various urinary symptoms according to CLSS (Q1, diurnal frequency; Q2, nocturia; Q3, urgency; Q4, urgency incontinence; Q6, slow stream; QoL index) after the nutritional guidance. On the other hand, the F group's urinary symptoms significantly worsened according to CLSS (Q1, diurnal frequency; Q2, nocturia; Q3, urgency; Q4, urgency incontinence; QoL index) after 12 weeks.

TABLE 3 Changes in salt intake volume and urological parameters between two groups

	Success group			Failure group		
	OW	12W	*P*-value	OW	12W	*P*-value
*SUNa (mEq/L)	115.4 ± 50.9	90.4 ± 40.0	<0.001	108.7 ± 49.0	114.7 ± 52.9	0.213
Estimated 24-hr Urinary Na excretion (mEq/day)	181.9 ± 39.3	135.0 ± 38.1	<0.001	163.2 ± 23.3	186.3 ± 34.3	<0.001
Estimated daily salt intake (g/day)	10.7 ± 2.3	8.0 ± 2.1	<0.001	9.6 ± 1.3	11.0 ± 1.8	<0.001
Daytime frequency	7.7 ± 2.4	6.4 ± 2.0	<0.001	7.6 ± 2.5	8.4 ±2.6	<0.001
Nighttime frequency	2.3 ± 0.9	1.4 ± 1.0	<0.001	2.3 ± 1.1	2.7 ± 1.1	<0.001
Fluid intake volume (ml/day)	2287.5 ± 577.1	1982.4 ± 524.3	<0.001	2262.2 ± 589.2	2540.3 ± 604.9	<0.001
Voided volume (ml)	244.4 ± 24.5	255.8 ± 30.8	<0.001	241.9 ± 24.7	238.7 ± 23.0	<0.001
Diurnal urine volume (ml)	1679.7 ± 492.0	1412.5 ± 406.1	<0.001	1636.1 ± 494.9	1821.9 ± 505.6	<0.001
Nocturnal urine volume (ml)	702.0 ± 185.4	538.8 ± 195.0	<0.001	705.1 ± 227.5	781.6 ± 224.1	<0.001
Nocturnal polyuria index (%)	30.2 ± 7.5	27.7 ± 7.3	<0.001	30.8 ± 8.3	30.5 ± 7.9	0.583

*Na concentration in the spot urine.

TABLE 4 Changes in core lower urinary tract symptom score after nutrition guidance

	Success group			Failure group		
	0W	12W	*P*-value	0W	12W	*P*-value
Q1. Diurnal frequency	0.8 ± 0.9	0.4 ± 0.7	<0.001	0.9 ± 1.0	1.1 ± 0.9	<0.001
Q2. Nocturia	1.9 ± 0.6	1.3 ± 0.8	<0.001	1.9 ± 0.6	2.0 ± 0.6	0.041
Q3. Urgency	1.0 ± 1.0	0.9 ± 1.0	0.001	1.0 ± 0.9	1.2 ± 0.9	< 0.001
Q4. Urgency incontinence	0.7 ± 0.9	0.6 ± 0.9	<0.001	0.6 ± 0.8	0.9 ± 0.9	<0.001
Q5. Stress incontinence	0.6 ± 0.9	0.6 ± 0.9	0.218	0.5 ± 0.8	0.5 ± 0.8	0.993
Q6. Slow stream	1.3 ± 1.1	1.2 ± 1.1	0.039	1.3 ± 1.1	1.3 ± 1.1	0.259
Q7. Strain	1.0 ± 1.2	0.9 ± 1.1	0.382	0.9 ± 1.1	1.0 ± 1.2	0.145
Q8. Incomplete emptying	0.9 ± 1.1	0.9 ± 1.1	0.141	0.8 ± 1.0	0.8 ± 1.0	0.405
Q9. Bladder pain	0.3 ± 0.7	0.3 ± 0.7	0.526	0.3 ± 0.6	0.3 ± 0.7	0.275
Q10. Urethral pain	0.2 ± 0.6	0.2 ± 0.6	0.082	0.2 ± 0.5	0.2 ± 0.5	0.310
QoL index	3.6 ± 1.2	2.7 ± 1.3	<0.001	3.2 ± 1.2	3.7 ± 1.4	<0.001

QoL, quality of life.

4 | DISCUSSION

The present study showed that the reduction of daily salt intake was effective for the improvement of LUTS, including nocturia, in patients with excessive salt intake. In addition, the patients who failed salt intake restriction had no changes in symptoms or worsened after the study period even though they also received nutritional guidance once every four weeks. Furthermore, the S group had decreased NUV and NPi after 12 weeks of nutritional guidance.

Nocturia is reported to be the most bothersome symptom among LUTS, and various factors contribute to its occurrence.[20] In this study, we paid special attention to changes in LUTS by reducing the daily salt intake in patients with excessive salt intake. We then performed a prospective study to clarify this issue for the first time.

Our results demonstrated that daytime frequency and nocturia significantly improved in patients who successfully reduced their salt intake (S group). In addition, we also showed that diurnal urine volume, NUV, and NPi also significantly decreased through nutritional guidance in the S group. The amount of salt intake is closely associated with fluid intake via stimulation of the thirst center in the brain through increased plasma sodium levels, increased transfer of fluid from the intracellular to the extracellular space, and activation of the renin-angiotensin system.[21–22] From these facts, there is a possibility that decreasing fluid intake mainly affected the results of this study. In short, we speculated that decreasing fluid intake by reduction of salt intake led to the improvement of LUTS in the S group. On the other hand, we also speculated that the decrease in peripheral edema through the reduction of salt intake may play an important role for the improvement of urine volume because edema is positively associated with NUV and NPi.[7,23,24] However, the patients with failed salt intake restriction had increased water intake volume, nighttime frequency, and NUV after the 12-week study period. Tani et al[7] reported that patients with water intake restriction who drink fluid heavily have decreased nighttime frequency and NUV. They also reported that the decreased diurnal water intake volume is positively correlated to the decreased NUV,[7] which is consistent with our results, wherein the increased water intake volume worsened the nighttime frequency and NUV of patients in the F group.

Our results as expected, showed decreased daytime frequency and nocturia due to reduction of salt intake. On the other hand, the finding that urgency and urinary incontinence, which are the important components of an overactive bladder, improved after the nutritional guidance in salt reduction was unexpected. In addition, the voided volume improved after the 12-week study period in the S group. Although the differences in voided volume were very small, we still consider that this result was very impressive, because this may indicate that the increased bladder volume might result in improvement in urinary frequency and the subjective storage symptoms according to CLSS score. Unfortunately, our study design cannot provide causation for this phenomenon. However, several investigators reported that excessive salt intake is associated with the imbalance of sympathetic and parasympathetic activities.[25,26] Furthermore, although the relationship between oxidative stress and excessive salt intake was well researched using an animal model, there is the opinion that excessive oxidative stress which could be caused by salt intake may affect the overactive bladder and manifest as urgency and urinary incontinence.[27,28] In short, oxidative stress altered the physiological function of the urothelium and increased bladder sensitivity or sense of urgency in in vivo and in vitro studies, and salt intake was associated with the excessive production of oxidative stress.[29] On the other hand, basic research reported that high salt loading induces urinary storage dysfunction via the upregulation of epithelial sodium

channel alpha in the bladder epithelium in Dahl salt-sensitive rats.[30] Thus, we believe that urgency and urinary incontinence by excessive salt intake are regulated by complex mechanisms.

There were some limitations in the present study. The number of patients was relatively small, and we could not determine the accurate proportion of the patients with peripheral edema, which is thought to affect nocturnal urine production. However, this study is the first report that evaluated the efficacy of salt restriction for urinary conditions, including nocturia, in human patients. Therefore, we believe that our results are important for discussing treatment strategies in patients with LUTS, especially in patients with excessive salt intake. Another limitation is that we did not evaluate the patients' sleeping hours despite its effects on physical conditions and mental health regardless of urinary conditions, including nighttime frequency. In addition, changes in oxidative stress, cytokines, and hormones by reduction of salt intake as well as statistical adjustments for the 12-week reduction in urine output were not analyzed. Furthermore, sodium intake was not monitored and recorded in the 3-day diary. Although we think such analyses are necessary to clarify the detailed roles and molecular mechanisms of salt reduction, this was beyond the scope of our study. Further detailed investigations including these issues are important for understanding the usefulness of salt reduction as a treatment strategy in patients with LUTS.

Finally, we emphasized that reduction of salt intake is safe and useful for health maintenance, and in the treatment of other diseases, including cardiovascular and cerebrovascular diseases, and not only limited to urinary conditions. In addition, salt reduction is a very reasonable procedure and does not require special instruments and comes at a low-cost compared to medications and other treatment methods. Therefore, we believe that our results are widely useful for discussing treatment strategies for patients with LUTS worldwide.

5 | CONCLUSIONS

Our results suggest that reduction of salt intake might be effective for LUTS patients who have nocturia with excessive salt intake. In addition, we also found that daytime frequency, urinary urgency, and urinary incontinence were also improved along with salt intake reduction. Furthermore, the success of the salt intake restriction might also induce the decrease in NUV, NPi, and fluid intake volume on FVC. Hence, our results support salt intake restriction as a treatment strategy for patients with LUTS, including those with nocturia. In addition, our results support the importance of randomized clinical trials with larger populations and the appropriate inclusion/exclusion criteria to conclude the clinical usefulness of salt reduction for these patients.

AUTHORS' CONTRIBUTIONS

Y Miyata contributed in project development, data analysis, manuscript writing. T Matsuo in data collection and manuscript writing. H Sakai in project development.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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