Daily salt intake is associated with leg edema and nocturnal urine volume in elderly men

Abstract

Aims:

There is accumulating evidence that excessive salt intake contributes to nocturnal polyuria. We aimed to investigate the relationship between salt intake, leg edema, and nocturnal urine volume to assess the etiology of nocturnal polyuria.

Methods:

A total of 56 men aged ≥60 years who were hospitalized for benign prostatic hyperplasia or with suspected prostatic cancer were enrolled. Urine frequency-volume charts of the patients were maintained, and they underwent bioelectrical impedance analysis twice daily (at 5 pm and 6 am) and examination of blood (brain natriuretic peptide levels) and urine (sodium and creatinine levels and osmotic pressure) samples once daily (at 6 am). Free water clearance, solute clearance, and sodium clearance at night were measured, and daily salt intake was estimated.

Results:

The data of 52 patients were analyzed. Daily salt intake positively correlated with leg edema at 5 pm, differences in leg extracellular fluid levels between 5 pm and 6 am, and nocturnal urine volume, but not with diurnal urine volume. Partial correlation coefficients showed that salt intake was a factor of the correlation between nocturnal urine volume and change in extracellular volume in the legs between 5 pm and 6 am. A multivariate logistic model showed that sleep duration and sodium clearance were independent predictive factors for nocturnal polyuria.

Conclusions:

Sodium intake correlates with diurnal leg edema and nocturnal urine volume in elderly men. These results provide evidence supporting sodium restriction as an effective treatment for nocturnal polyuria.

Keywords: Leg, edema, sodium, urine, nocturia

Introduction

In 2002, the International Continence Society (ICS) defined nocturia as a "complaint" associated with nighttime voiding. In 2018, this definition was changed to include the "number of times" urine is passed during the main sleep period.[1] The prevalence of nocturia is high, particularly among the elderly. Among men aged >70 years, the prevalence rate is one or more voiding events in 68.9–93% and two or more voiding events in 29–59.3% of the demographic population.[2] The prevalence of two and more voiding events affects health-related quality of life.[3] Nocturia is associated with bone fractures and mortality.[4] These findings suggest that nocturia should be adequately managed. Nevertheless, nocturia treatment in the elderly is often difficult because of the multiple etiologies for the condition.[5] Nocturia is strongly associated with nocturnal polyuria,[6] which is also associated with hypertension.[7, 8] Excessive dietary salt intake is one of the important risk factors for hypertension.[9] Daily salt intake is associated with nocturia, and provision of guidance for salt intake restriction leads to improvement in nocturia.[10, 11] Nocturnal polyuria is associated with leg edema.[12, 13] One of the major causes of edema is increased plasma volume, secondary to sodium and water retention.[14] The extent of leg edema is correlated with nocturnal urine volume (NUV).[12,15] Therefore, we hypothesized that salt intake might be associated with leg edema and NUV. There have been no reports directly investigating the relationships among these three factors. Therefore, in the present study, we determined the relationships among salt intake, leg edema, and NUV in elderly men.

Materials and methods

Male patients aged ≥60 years and scheduled to be hospitalized for transurethral resection of the prostate or prostate biopsy were enrolled. The patients who presented with the following conditions were excluded: serum creatinine >1.5 mg/dL, fasting blood sugar >200 mg/dL, New York Heart Association classes 2–4, Child-Pugh grades A to C, sleep-disordered breathing, post-void residual urine >100 mL, urinary tract infection, and regular use of diuretics.

The patients maintained a 24-h urine frequency-volume chart from 8 am on the day before hospitalization. Urine was sampled at 6 am. Blood examinations (aldosterone, brain natriuretic peptide, and osmotic pressure) and bioelectrical impedance analyses (BIA) were conducted at the beginning of the hospitalization. Nocturnal diuresis was evaluated based on free water clearance and solute clearance. These clearances were measured from a first-morning-void urine sample.[12] We collected only the first-morning-void urine sample for analysis. The 24-h Na excretion can be estimated by measuring the Na/creatinine (Cr) ratio in the second-morning-urine sample.[16] It is a reliable method by which nocturnal sodium diuresis can be estimated using the first-morning-urine sample. According to the ICS, NUV is the total volume of urine produced during the individual's main sleep period, including the first void in the morning.[1] Nocturnal polyuria was defined as [nocturnal urine volume]/[24 h urine volume] >0.33.[17]

The estimated sodium intake for 24 h was calculated using the following formula: 21.98 × [sodium in spot urine (mEq/L)/creatinine in spot urine (mg/dL)/10 × estimated 24-h urinary excretion of creatinine (mg/day)]$^{0.392}$/17. The estimated 24-h urinary excretion of creatinine (mg/day) was calculated using the following formula: [body weight (kg) × 14.89] + [height (cm) × 16.14] – (age × 2.043) – 2244.45. Plasma osmotic pressure was calculated using the following formula: Sodium (mEq/L) × 2 + glucose (mg/dL)/18 + urea nitrogen (mg/dL)/2.8. Free water clearance was calculated as follows: (1 – [urine osmotic pressure (osm)]/[plasma osmotic pressure (osm)]) × [urine flow (mL/min)]/[body surface area (m^2)].

BIA was performed using InBody S10® (InBody Japan, Tokyo, Japan). Low frequencies tend to flow outside the cell membrane, while higher frequencies flow both inside and outside. In other words, low frequencies reflect the extracellular fluid (ECF), and high frequencies reflect the total body fluid. The use of a single low frequency is incapable of determining the fluid inside the cell. However, with the multifrequency method, it is possible to measure total body fluid accurately. Intracellular fluid can be calculated using the measured ECF and total body water.[17] ECF levels were evaluated at 5 pm and 6 am because a previous study showed that the volume of ECF was significantly greater at 5 pm in patients with nocturnal polyuria than in the control group. It was also reported that volume was the smallest at the wake-up time in both groups.[12] Correlations between salt intake, leg edema, and NUV were analyzed using Spearman's correlation coefficient by rank, and partial correlation coefficients were calculated. Univariate and multivariate analyses were conducted using age, body mass index, 24-h salt intake, serum sodium, blood glucose, serum creatinine, brain natriuretic peptide, urine osmotic pressure, plasma osmotic pressure, sleep duration, 24-h water intake, water intake from 6 pm to 10 pm, free water clearance, sodium clearance, osmotic clearance without sodium, leg edema at 5 pm, and the difference in leg ECF volume between 5 pm and 6 am. A P-value < 0.05 was considered statistically significant. Values were expressed as mean ± standard deviation. IBM SPSS ver. 24 was used for all statistical analyses.

This study was approved by the Institutional Review Board. Written informed consent for the clinical study was obtained from all patients prior to registration.

Results

Patient characteristics

A total of 56 patients were enrolled. Two patients did not accurately maintain the frequency-volume diaries, and two patients did not undergo BIA. Finally, the data of 52 patients were analyzed. The mean age was 68.5 ± 5.5 years. No patients had renal dysfunction (serum creatinine 0.89 ± 0.2 mg/dL), heart failure (BNP 23.2 ± 23.3 pg/dL), or water intake >2500 mL/day (Table 1).

Correlation of parameters with salt intake, changes in extracellular fluid volume, and nocturnal urine volume

Salt intake correlated with edema ([ECF volume]/[total cellular fluid volume]) in the trunk and legs, but not with the total ECF volume at 5 pm. Salt intake correlated with the difference in ECF in legs between 5 pm and 6 am. It also correlated with the 24-h urine volume, NUV, and sodium clearance. The change in ECF correlated with NUV. NUV correlated with sodium and osmotic pressure clearance (Table 2).

Partial correlation between parameters

When the influence of the change in ECF volume was excluded, salt intake correlated with NUV. When the influence of NUV was excluded, the change in ECF volume correlated with salt intake. However, when the influence of salt intake was excluded, the change in ECF did not correlate with NUV (Table 3).

Independent influence factors of nocturnal polyuria

Multivariate analysis revealed that sleep duration and sodium clearance were directly associated with nocturnal polyuria (Table 4).

Discussion

We aimed to measure correlations among salt intake, leg edema, and NUV in elderly men and found that salt intake correlated with leg edema and NUV. Nocturnal polyuria is defined as excessive production of urine during the individual's main sleep period.[18] The production of urine is related to the sum of free water clearance and osmotic pressure clearance. Nocturnal polyuria is caused by excess free water clearance or osmotic pressure clearance. Osmotic pressure clearance is the excretion of water when solutes, including glucose, sodium, and urea, that generate osmotic pressure are excreted in the kidney. In the present study, we did not enroll patients with diabetes or urinary glucose positivity to minimize the influence of glucose. We calculated the clearances, dividing into osmotic pressure clearance by sodium and other osmotic pressure clearances. In healthy adults, sodium intake equals sodium excretion, and over 90% of sodium is excreted in the urine when no intense sweating occurs. Therefore, increased sodium intake leads to increased urine production.[19]

Typical nocturnal polyuria involves a decrease in urine production during the daytime, which causes water accumulation in legs as edema. We found that sodium intake positively correlated with leg edema at 5 pm. Diurnal edema formation may decrease circulating plasma volume, stimulating the renin-angiotensin system and sympathetic nervous system in the kidney; and sodium reabsorption is increased to maintain circulating plasma volume. Although diurnal sodium excretion was not measured in the present study, diurnal sodium excretion was reported to decrease in patients with nocturnal polyuria.[20]

The source of nocturnal urine is water accumulated in legs until bedtime. When lying in bed, the hydrostatic pressure in the lower limb vein decreases, and water and sodium stored in the cell stroma move into veins. This leads to increased circulating plasma volume, which increases urinary production. In the present study, NUV, the change in ECF volume in legs between 5 pm and 6 am, and sodium intake positively correlated with one another. However, NUV did not correlate with the change in ECF volume in legs when the influence of sodium intake was excluded. These findings suggest that sodium intake is necessary for the increase in NUV.

We did not find any correlation between sodium intake and water clearance. We previously reported that leg edema negatively correlated with arginine vasopressin secretion in elderly men.[13] In that study, we did not investigate sodium intake. As water moves from the interstitium of the legs into the blood vessels, sodium is also transported in the recumbent position, maintaining plasma osmotic pressure and not affecting water clearance. Sodium intake transiently increases plasma osmotic pressure, stimulating the hypothalamus and increasing water intake, possibly increasing water clearance. Independent factors affecting nocturnal polyuria were sodium clearance and sleep duration. This result is reasonable because longer sleep duration may lead to longer periods of urine production, and sodium excretion may also increase urine production.

In the present study, free water clearance was not an independent factor affecting nocturnal polyuria. Patients with severe symptoms of nocturnal polyuria tended to have high urine volume early at night. Free water clearance might be an independent factor if we consider the urine voided early at night instead of urine at the first-morning void as a variable. Unfortunately, we could not check this result because we sampled urine only at the first-morning void.

Our results might vary with the definition of nocturnal polyuria. We used the nocturnal polyuria index (NPi), which estimates the proportion of NUV to the 24-h urine volume, as the definition of nocturnal polyuria. Previous studies on nocturnal polyuria have used other definitions: NUV >0.9 mL/min (NUV 0.9)[21] and nocturnal urine production >90 mL/h (NUP 90).[22] It has been reported that NUP 90 may be a more specific parameter for nocturnal polyuria. Although the data of urine production between 1 am to 6 am have been used to estimate NUP 90, we could not do so in this study because the lack of accurate data regarding urine production for 6 hours. Therefore, we recalculated our data using NUV 0.9, as shown in the Supplementary Table. Interestingly, the difference between the nocturnal polyuria and non-nocturnal polyuria groups changed when using NPi. The mean urine osmotic pressure was significantly lower in the nocturnal polyuria group. The mean 24-h water intake, 24-h urine volume, and NUV were significantly higher in the nocturnal polyuria group. Multivariate analysis revealed that sodium clearance was an independent factor for nocturnal polyuria based on NUV 0.9 (odds ratio 16.836, 95% confidence interval 1.3 to

217.9, p= 0.031).

The present study had some limitations. First, although the sample size may have been small, but we achieved statistically significant results. Second, we used data from a one-day urine frequency-volume chart. Although only the 3-day frequency-volume chart has been validated for estimating nocturia, we believe that short duration data are sometimes needed to make studies realistic and feasible. Third, we did not evaluate the renin-angiotensin-aldosterone system that regulates blood pressure and ECF volume. Fourth, we did not measure diurnal sodium clearance that influences nocturnal sodium clearance. Finally, over half (39 of 52) of the patients woke up to void at least once. Most patients emptied their bladder at 1:00 am or later and consequently reduced their free-water clearance peak. This might have reduced the reliability of the statistical analyses. Despite these limitations, the present study suggests that excessive salt intake may increase leg edema, suggesting limited diurnal urine production, leading to nocturnal urine production with increased sodium excretion in elderly men.

Conclusions

Sodium intake is positively associated with diurnal leg edema and NUV in elderly men. This result supports the notion that sodium restriction is an effective treatment for nocturnal polyuria. This may be more important for patients with risk factors for nocturnal polyuria such as renal dysfunction, heart failure, and hypertension. Patients with these complications should be investigated in future studies.

Acknowledgments

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