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Twenty-four-hour urine osmolality as a representative index of adequate hydration and a predictor of recurrence in patients with urolithiasis

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Abstract

Purpose To determine the value of 24-h urine osmolality (UOsm) as a representative index of adequate hydration and predictor of stone recurrence in patients with urolithiasis.

Methods Medical records of consecutive patients presenting with renal or ureteric stones between 1994 and 2017 were retrospectively reviewed. Patients were grouped according to the results of 24-h UOsm (low ≤ 564 mOsm/kg H_2O, high > 564 mOsm/kg H_2O). Metabolic parameters and risk of stone recurrence were compared between the two groups.

Results The low urine concentration group were more likely to be older, to be female, and to have a lower body mass index and higher glomerular filtration rate than the high concentration group (each $P < 0.005$). A positive correlation was seen between 24-h UOsm and urinary calcium, sodium, uric acid, and magnesium excretion and 24-h specific gravity; a negative correlation was seen with 24-h urine volume. Stone-forming constituents, such as calcium and uric acid, were significantly higher in the high urine concentration group. Kaplan–Meier estimates showed that the low urine concentration group had a significantly longer stone recurrence-free period than the high urine concentration group (log-rank test, $P < 0.001$). In multivariate Cox regression analyses, 24-h UOsm was seen to be an independent risk factor for stone recurrence.

Conclusions UOsm is a promising approach to assessing hydration and predicting stone recurrence in patients with urolithiasis. Maintaining UOsm < 564 mOsm/kg H_2O may reduce the risk of stone recurrence.

Keywords Urinary calculi · Osmolar concentration · Recurrence

Introduction

The prevalence of urolithiasis is reported to be 2–20%, with variations seen between populations and geographic regions; recent data indicate that the global prevalence is increasing [1–3]. Urolithiasis is associated with a high recurrence rate of 30–50% within 10 years of the first stone episode [4, 5]. This can have a major economic impact secondary to the cost of treating recurrent episodes of renal colic and intervention-related morbidity [6]. Therefore, the prevention of stone recurrence can be considered to be as important as the initial treatment. Individualized metabolic investigation, dietary recommendations, and medical treatment should, therefore, be offered to prevent or reduce the stone recurrence [7–9].

Low urine volume and a high urine concentration are regarded as important lithogenic factors in the development of urolithiasis [10, 11]. Since the urinary concentration of

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stone-forming salts is strongly affected by the daily urine volume, increasing the daily fluid intake is an important factor in preventing recurrent stone disease [12–14]. Indeed, the results of a randomized controlled trial showed that higher fluid intake reduces the risk of stone formation [15]. Although current guidelines recommend a fluid intake of at least 2 L per day, other factors (such as insensible loss and water contained in foods) can also influence urine volume [13, 16]. Urinary output and urine concentration reflect the antidiuretic activity required to maintain water balance in response to varying levels of water intake and loss [16, 17]. Therefore, a representative index of a patient's hydration status is of particular interest as it defines the probability of stone recurrence and is required to determine the patient's compliance with dietary modifications for the prevention of stone formation.

Evaluation of 24-h urine osmolality (UOsm) is the biomarker most suitable for determining appropriate individual fluid intake as it reflects the net sum of water gains, water losses, and neuroendocrine regulatory responses [16, 18]. Despite widespread use, the validity of UOsm to assess hydration status and predict stone recurrence risk has not been adequately evaluated. Therefore, the aim of this study was to investigate the value of UOsm as a representative urinary index of hydration status and as a predictor of stone recurrence in patients with urolithiasis.

Materials and methods

Study population

Data from 5724 patients presenting with renal or ureteric stones at our institution between January 1, 1994, and December 30, 2017, were retrospectively analyzed. Patients were excluded if they were < 18 years of age, or had incomplete 24-h urine collection data (creatinine < 17 mg/kg per 24 h for men and < 13 mg/kg per 24 h for women), impaired renal function (serum creatinine > 1.5 mg/dl), bladder stones, urethral stones, staghorn calculi, urinary tract obstruction, malformation of the urological system, or metabolic disease that may affect calcium and bone metabolism. Exclusion criteria also included prior vasopressin therapy as this may affect urine concentration.

The study protocol was reviewed and approved by the institutional review board of the Chungbuk National University Hospital. The requirement for informed consent was waived due to the retrospective nature of the study.

Measurements and definitions

After urine centrifugation, UOsm was measured by freezing point depression, using an osmometer (Model 2020, Advanced Instruments, Norwood, MA, USA). Metabolic evaluation was conducted at least 4 weeks after the stone episode. Any medications that could affect serum and 24-h urine chemistry results were discontinued at least 2 weeks prior to metabolic evaluation. The risk of urinary stones was evaluated by assessing the following parameters: sodium (ion-selective electrode method), calcium (o-Cresolphthalein complex), uric acid (uricase colorimetry method), oxalate (oxalate oxidase method), citrate (citrate lyase method), and magnesium (xylidyl blue method). Serum creatinine levels were used to calculate baseline creatinine clearance according to the formula proposed by Cockcroft and Gault [19]. Creatinine clearance was corrected by a factor of 0.85 for women to account for differences in lean body mass.

Follow-up protocol

All patients were instructed to follow a recommended diet, i.e., reduced animal protein and salt, increased fruit and vegetables, restricted intake of oxalate-rich foods, and increased fluid intake (≥ 2 L/day); none were placed on a low-calcium diet. At the initial follow-up visit, all patients underwent detailed radiologic imaging, such as plain film, abdominal ultrasonography, and computerized tomography (CT) scan. It was recommended that patients be followed up every 6 months. At each visit, all patients underwent radiologic evaluation and an obscure stone was confirmed by CT scan. Stone recurrence was defined as the radiographic appearance of stones that were not present at the previous examination. The time to stone recurrence was the time interval between the preceding examination and the most recent examination where the new stone was detected.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD). The relationship between 24-h UOsm and 24-h urine metabolic profile was assessed using Pearson correlation coefficients and covariate-adjusted partial correlation coefficients. Receiver operating characteristic (ROC) curves were constructed to identify the UOsm cutoff value that would confer optimal sensitivity and specificity for the prediction of recurrence (564 mOsm/kg H_2O; Supplementary Figure). The differences between groups in terms of urine variables were assessed using the Mann–Whitney *U* test. Categorical variables were compared using the Chi-square or Fisher's exact test, as appropriate. The Kaplan–Meier method was used to calculate time to recurrence, and differences were assessed using the log-rank test. Univariate and multivariate survival analyses were performed using the Cox proportional hazard regression model. All statistical analyses were performed using SPSS® 24.0 software

(IBM, Armonk, NY, USA), and all tests were two-tailed. A P value < 0.05 was considered to be statistically significant.

Results

Twenty-four-hour urine collection data for the metabolic evaluation and assessment of UOsm were available for 2,142 patients (37.4% of the total cohort) and 808 patients (14.1% of the total cohort), respectively. Following exclusions, data for 680 patients were included in the analysis (low urine concentration group, $n = 400$; high urine concentration group, $n = 280$).

Comparison of demographic and stone variables according to 24-h urine osmolality

The low urine concentration group were more likely to be older, to be female, and to have a lower body mass index and higher glomerular filtration rate then the high urine concentration group (each $P < 0.005$). No significant differences were seen in the presence of hypertension or diabetes mellitus, personal stone history, stone location, and stone composition (all $P > 0.05$; Table 1).

Association between 24-h urine osmolality and 24-h urine constituents

A positive correlation was seen between 24-h UOsm and urinary calcium ($r = 0.142$, $P < 0.001$), sodium ($r = 0.120$, $P = 0.002$), uric acid ($r = 0.085$, $P = 0.028$), and magnesium ($r = 0.078$, $P = 0.044$) excretion, and 24-h specific gravity (SG; $r = 0.711$, $P < 0.001$); a negative correlation was seen with 24-h urine volume ($r = -0.513$, $P < 0.001$; Table 2; Fig. 1). In comparison with the high urine concentration, subjects with a low urine concentration had significantly lower levels of urinary calcium, sodium, uric acid, and magnesium excretion; urine volume was significantly higher (each $P < 0.005$). There was no significant difference in

Table 1 Baseline patient characteristics

Parameters	UOsm ≤ 564 mOsm/kg H_2O (n = 400)	UOsm > 564 mOsm/kg H_2O (n = 280)	P value
Mean age, years ± SD	51.29 ± 45.88	45.88 ± 15.01	< 0.001*
Mean BMI, kg/m^2	24.07 ± 3.69	25.23 ± 3.85	< 0.001*
Sex, n (%)			< 0.001†
Male	214 (53.5)	195 (69.6)	
Female	186 (46.5)	85 (30.4)	
Hypertension, n (%)			0.229†
Yes	109 (29.6)	60 (25.0)	
No	259 (70.4)	180 (75.0)	
Not available	32	40	
Diabetes mellitus, n (%)			0.091†
Yes	67 (18.3)	31 (12.9)	
No	300 (81.7)	209 (87.1)	
Not available	33	40	
Previous stone history, n (%)			0.864†
FSF	284 (71.0)	116 (29.0)	
RSF	197 (70.0)	83 (29.6)	
Stone location, n (%)			0.146†
Kidney	89 (22.2)	49 (77.8)	
Ureter	311 (77.8)	231 (82.7)	
Stone composition, n (%)			0.661
Calcium oxalate	142 (66.4)	88 (67.7)	
Uric acid	55 (25.7)	35 (26.9)	
Calcium phosphate	17 (7.9)	7 (5.4)	
Not available	186	150	
Mean GFR, mL/min per 1.73 m^2 ± SD	74.72 ± 41.39	86.10 ± 35.24	< 0.001*

BMI body mass index, *FSF* first stone former, *GFR* glomerular filtration rate, *RSF* recurrent stone former, *SD* standard deviation, *UOsm* urine osmolality

P values are based on the *Mann–Whitney U test and †Fisher's exact test

Table 2 Correlation between 24-h urine osmolality and 24-h urine constituents

Parameters	*r*	*P* value
Calcium, mg/day	0.142	< 0.001
Sodium, mg/day	0.120	0.002
Uric acid, mg/day	0.085	0.028
Oxalate, mg/day	− 0.052	0.181
Citrate, mg/day	0.017	0.664
Magnesium, mg/day	0.078	0.044
Urine specific gravity	0.711	< 0.001
Urine volume, mL/day	− 0.513	< 0.001

r is the partial correlation coefficient adjusted by age, sex, body mass index, and calculated glomerular filtration rate

P values are based on partial correlation analysis

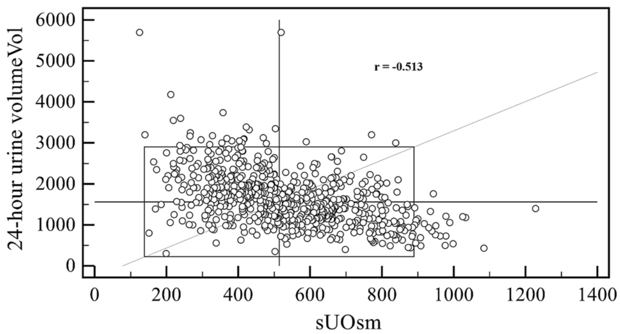

Fig. 1 Correlation between 24-h urine osmolality and 24-h urine volume. **P* values are based on partial correlation analysis; *r* = partial correlation coefficient adjusted by age, sex, body mass index, and calculated glomerular filtration rate

urinary oxalate or citrate excretion between the two groups (both $P > 0.05$; Table 3).

Stone recurrence according to 24-h urine osmolality

Kaplan–Meier curves showed a significant difference between the low and high urine concentration groups in terms of stone recurrence; patients with low urine concentrations had a significantly longer stone recurrence-free period than those with high urine concentrations (log-rank test, $P < 0.001$; Fig. 2).

Table 4 shows the results of univariate and multivariate Cox proportion hazard analysis for the prediction of stone recurrence. In the univariate analysis, female sex, 24-h urine volume, and 24-h UOsm as a continuous or categorical variable was associated with stone recurrence. In the multivariate analysis, 24-h UOsm, as a continuous [hazard ratio (HR) 1.001; 95% confidence interval (CI), 1.000–1.003; $P = 0.024$] or categorical (HR 1.828; 95% CI 1.149–2.909; $P = 0.011$) variable, was seen to be the only risk factor for stone recurrence.

Discussion

This study assessed the value of 24-h UOsm as a representative index of hydration status and a predictor of stone recurrence in patients with urolithiasis. A positive correlation was seen between 24-h UOsm and 24-h SG, whereas a negative correlation was seen with 24-h urine volume. Stone-forming constituents, such as calcium and uric acid, were significantly lower in the low urine concentration group. More importantly, 24-h UOsm was seen to be an independent risk factor for stone recurrence, as both a continuous and a categorical variable. Therefore, 24-h UOsm appears to be

Table 3 Comparison of 24-h urine constituents according to 24-h urine osmolality

Parameters	UOsm ≤ 564 mOsm/kg H_2O (*n* = 400)	UOsm > 564 mOsm/kg H_2O (*n* = 280)	*P* value
Calcium, mg/day	149.61 ± 94.53	193.15 ± 101.97	< 0.001*
Sodium, mg/day	157.58 ± 74.42	180.99 ± 74.90	< 0.001*
Uric acid, mg/day	545.09 ± 196.42	620.49 ± 252.81	< 0.001*
Oxalate, mg/day	28.23 ± 25.79	26.31 ± 16.60	0.276*
Citrate, mg/day	381.21 ± 267.56	401.21 ± 221.32	0.307*
Magnesium, mg/day	86.92 ± 40.21	93.36 ± 38.88	0.038*
Urine volume, mL/day	1860. 03 ± 685.24	1341.33 ± 514.73	< 0.001*
Urine volume, L/day			< 0.001†
< 1.5	119 (29.8)	189 (67.5)	
≥ 1.5	281 (70.2)	91 (32.5)	

Data are presented as mean ± standard deviation or *n* (%)

UOsm urine osmolality

P values are based on the *Mann–Whitney *U* test and †Fisher's exact test

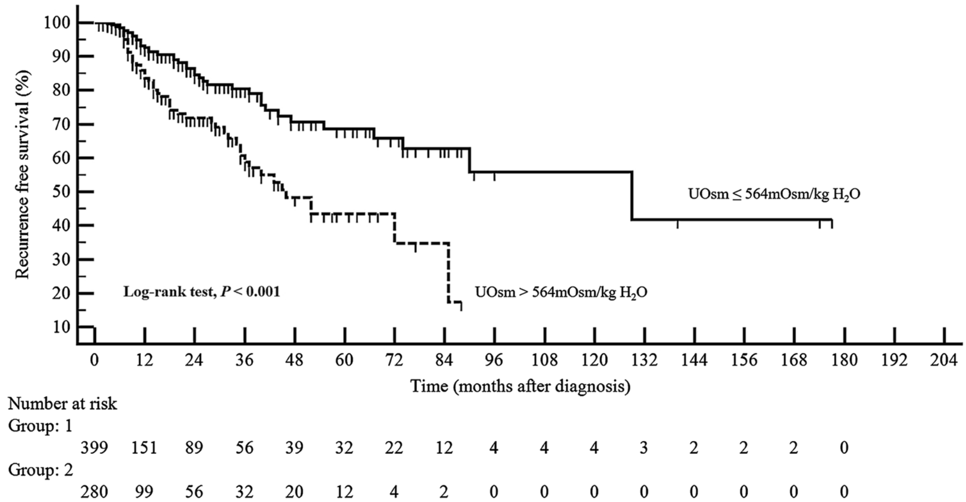

Fig. 2 Stone-recurrence-free survival according to 24-h urine osmolality (UOsm; UOsm ≤ 564 mOsm/kg H_2O vs. UOsm > 500 mOsm/kg H_2O)

Table 4 Multivariate Cox regression analysis of the probability of stone recurrence

Variables	Univariate analysis		Multivariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	0.987 (0.974–1.000)	0.051	–		–	
Sex (female)	0.574 (0.371–0.888)	0.013	0.648 (0.410–1.023)	0.062	0.642 (0.408–1.009)	0.055
BMI, kg/m^2	1.038 (0.986–1.092)	0.154	–		–	
24-h urinary calcium, mg/day	1.002 (1.000–1.004)	0.096	–		–	
24-h urinary sodium, mg/day	1.002 (0.999–1.004)	0.207	–		–	
24-h urinary uric acid, mg/day	1.000 (0.999–1.001)	0.620	–		–	
24-h urinary oxalate, mg/day	0.996 (0.986–1.008)	0.531	–		–	
24-h urinary citrate, mg/day	1.000 (0.999–1.001)	0.885	–		–	
24-h urinary magnesium, mg/day	1.688 (0.325–8.769)	0.533	–		–	
24-h urine volume, mL/day	1.000 (0.999–1.000)	0.018	1.000 (0.999–1.000)	0.253	1.000 (0.999–1.000)	0.156
GFR, mL/min per 1.73 m^2	1.002 (0.998–1.007)	0.279	–		–	
24-h UOsm, mOsm/kg H_2O	1.002 (1.001–1.003)	< 0.001	1.001 (1.000–1.003)	0.024		
24-h UOsm, > 564 mOsm/kg H_2O	2.276 (1.495–3.463)	< 0.001			1.828 (1.149–2.909)	0.011

Multivariate Cox regression analysis was used to estimate hazard ratio (HR) with the corresponding 95% confidence interval (CI)

BMI body mass index, *GFR* glomerular filtration rate, *UOsm* urine osmolality

a valuable indicator of hydration status and a predictor of stone recurrence in patients with urolithiasis.

A low urine volume and high urine concentration are regarded as important risk factors for the development of urinary stones [8, 11, 20]. Therefore, a high fluid intake has generally been recommended as a prophylactic measure to produce more dilute urine and to prevent supersaturation and crystallization of lithogenous salts [14, 16, 17]. The benefit of increased fluid intake has been demonstrated in a prospective, randomized, controlled study of patients with a history of urolithiasis [15]. In this study, the intervention group was instructed to increase fluid intake to achieve a urine volume of at least 2 L/day with no further dietary changes, while the control group received no intervention. Over a 5-year follow-up period, the stone recurrence rate in the intervention group was significantly lower, with a longer time to first recurrence, than in patients who received no intervention. A recent economic analysis modeled on the French healthcare system suggests that the primary prevention strategy of ensuring a fluid intake of at least 2 L/day could prove to be a cost-effective approach, compared with no intervention [18]. Based on the evidence to date, recent guidelines recommend that the 24-h urine volume should exceed 2.0–2.5 L for a normal adult [1, 20]. However, the required level of fluid intake is difficult to maintain indefinitely [21]. To monitor and improve compliance with hydration therapy, representative urinary indices such as 24-h UOsm and SG have been validated as accurate markers of habitual total fluid intake [22–25]. In a study by Cadoff et al. [26], paper test strips were used to monitor urine pH and SG in patients with urolithiasis. Another study by Khorami et al. [21] also suggested that behavioral intervention through the measurement of urine SG using a dipstick test is an effective method of maintaining optimal urine volume. Urolithiasis guidelines developed by the European Association of Urology recommend that a urinary SG < 1.010 should be maintained [27]. In general, there is a good correlation between the SG and osmolality of a urine sample [28]. However, despite the convenience of the dipstick SG testing methods, urinary pH and the ionic composition of the urine can affect the results and their interpretation [29]. SG, as measured by refractometry, is influenced by proteinuria, glucosuria, and large molecules, such as radiographic contrast media or mannitol [29]. Voinescu et al. [28] previously studied the relationship between SG and osmolality in vitro using simulated urine specimens of varying composition, demonstrating that urine SG could over- or underestimate the UOsm under different clinical conditions.

Assessment of 24-h UOsm is regarded as the best biomarker of optimal hydration with respect to the risk of urolithiasis [25, 29]. While plasma osmolality is a biomarker that is sensitive to acute dehydration, it is maintained within a narrow range across a broad spectrum of daily fluid intake volumes [25]. Plasma osmolality represents the outcome (i.e., the successful maintenance of total body water and plasma osmolality), but not the process (i.e., antidiuresis via the urine concentrating mechanism) involved in maintaining body water balance [21, 22]. Therefore, urinary volume and, more specifically, UOsm are the end result reflecting the antidiuretic activity required to maintain water balance in response to varying levels of water intake and loss [2, 23, 30]. However, few studies have evaluated the validity of 24-h UOsm in the assessment of hydration status and prediction of individual stone recurrence risk. In the current study, 24-h UOsm was positively correlated with 24-h urine SG and negatively correlated with 24-h urine volume. In addition, the urinary excretion of lithogenous salts was significantly higher in the low urine concentration group, an observation that has also been made in a previous study [25]. The most important result of the present study was the finding that 24-h UOsm is an independent risk factor for stone recurrence. To our knowledge, this is the first study designed to evaluate the value of 24-h UOsm as a predictor of stone recurrence in patients with urolithiasis. Although 24-h UOsm is a relevant marker for stone recurrence, its use as a monitoring marker is limited because of the possibility of spilling urine and the impact on patients' daily activities. Therefore, additional studies are planned to determine whether spot urine UOsm can represent 24-h UOsm and predict stone recurrence in this patient group.

The main limitation of the current study is the retrospective, single-center design. As the susceptibility to urolithiasis appears to vary with climate, geographic location, and socioeconomic characteristics, it may not be possible to generalize our data to other populations. In addition, the threshold level of 24-h UOsm (564 mOsm/kg H_2O) was based on single-center experience and may be arbitrary. Additional, prospective studies will be required to ratify the results of this study and to confirm the 24-h UOsm thresholds for recurrence prevention. Despite the limitations, this study is the first to assess the value of 24-h UOsm for the prediction of stone recurrence in patients with urolithiasis. Our findings provide important evidence that can be used as part of a patient's recurrence risk assessment and to guide recommendations regarding adequate fluid intake.

Conclusions

This study identified a correlation between 24-h UOsm and both 24-h SG and 24-h urine volume. The high urine concentration group showed a number of lithogenic risk factors and a high probability of stone recurrence compared with the low urine concentration group. These results suggest that 24-h UOsm may serve as an optimal representative index of hydration status and a predictor of stone recurrence in patients with urolithiasis. Further investigation in a large, prospective study is required to validate our findings and to establish an appropriate 24-h UOsm threshold for adequate hydration.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent The requirement for informed consent was waived due to the retrospective nature of the study.

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