



A high basal metabolic rate is an independent predictor of stone recurrence in obese patients

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Purpose: Basal metabolic rate (BMR) is an indicator of overall body metabolism and may portend unique aberrations in urine physico-chemistry and stone recurrence. The present study examined the effect of predicted BMR on 24 hours urinary metabolic profiles and stone recurrence in obese stone patients.

Materials and Methods: Data from 308 obese patients (body mass index [BMI] ≥ 30 kg/m²) diagnosed with urinary stone disease between 2003 and 2015 were analyzed retrospectively. BMR was calculated using the Harris–Benedict equation, and patients were classified into two predicted BMR categories (<1,145 kcal/day, $\geq 1,145$ kcal/day). Urinary metabolic parameters and risk of stone recurrence were compared between the two groups.

Results: The high BMR group was more likely to be younger and female, and to have a high BMI and lower incidence of diabetes than the low BMR group (each $p < 0.05$). There was a positive correlation between BMR and 24 hours urinary sodium, uric acid, and phosphate excretion. The amounts of stone-forming constituents such as calcium and uric acid were significantly higher in the high BMR group. Kaplan–Meier estimates showed that the high BMR group had a significantly shorter stone recurrence-free period than the low BMR group (log-rank test, $p < 0.001$). Multivariate Cox regression analyses revealed that predicted BMR was an independent factor of stone recurrence (hazard ratio, 2.759; 95% confidence interval, 1.413–5.386; $p = 0.003$).

Conclusions: BMR may be an easily measured parameter that can be used to identify risk of stone recurrence in obese stone patients.

Keywords: Basal metabolism; Obesity; Recurrence; Urinary calculi

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INTRODUCTION

The prevalence and incidence of urolithiasis have increased in many countries in recent years. Although prevalence varies widely in different regions of the world, it depends greatly on geographic area, racial distribution,

socioeconomic status, and dietary habits [1,2]. In addition, urolithiasis tends to be recurrent, with rates of 50% in the majority of cases within 5 years since the first stone event [3,4]. Despite intensive research into the pathogenesis of stone formation, the factors associated with increased risk of recurrence remain unclear [5]. Identifying patients with re-

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current stones at the time of initial presentation could help to reduce both morbidity and costs through more comprehensive monitoring, such as precise imaging and biochemical evaluation, and through more aggressive preventive measures such as dietary, behavioral, and pharmacologic interventions [5,6].

Recently, it was suggested that urolithiasis may be a systemic disorder linked to the metabolic syndrome [1,7-9]. The prevalence of urolithiasis increases progressively and in parallel with the increase of the incidence of obesity, diabetes, dyslipidemia, and hypertension [8,10]. As a major component of metabolic syndrome, obesity has a significant impact on urinary metabolic risk factors [11-13]. Body mass index (BMI) serves as a suggestive surrogate for obesity, and many studies show that subjects with obesity (BMI of 30 kg/m² or higher) have an increased incidence of urolithiasis [13]. Although urolithiasis is strongly associated with obesity, numerous cases develop independently of body fatness. It is our hypothesis that not only body fatness, but also basal metabolic rate (BMR) (defined as the daily rate of energy metabolism required to preserve vital functions) may portend unique aberrations in urine physico-chemistry and stone recurrence. As far as we are aware, no study has examined the impact of BMR on the development of urolithiasis. Therefore, we examined aberrations in urine physico-chemistry and stone recurrence risk in stone formers according to BMR. Specifically, we focused on obese patients (BMI \geq 30 kg/m²) with urolithiasis since our preliminary analysis revealed that BMR is not a significant predictor of stone recurrence in underweight, normal, or overweight patients with urolithiasis.

MATERIALS AND METHODS

1. Study population

Data from 5,590 patients presenting with renal or ureteric stones at our institution between January 1, 2003 and December 30, 2015 were analyzed retrospectively. Patients were excluded if they were <18 years of age; lacked sufficient clinical information (i.e., height, body weight, stone history, presence of diabetes, or hypertension); had urethral stones or staghorn calculi; had urinary tract obstruction or malformation of the urological system; or had metabolic disease that may affect calcium and bone metabolism.

A preliminary analysis categorized patients into four groups according to BMI: less than 18.5 kg/m² (underweight), 18.5–24.9 kg/m² (normal weight), 25.0–29.9 kg/m² (overweight), and 30.0 kg/m² or more (obese). The ability of BMR to predict stone recurrence in patients with urolithiasis was calculated

using receiver operating characteristic (ROC) curves and areas under the ROC curve for the four BMI groups. BMR was not a significant predictor of stone recurrence in underweight, normal, or overweight patients with urolithiasis (Supplementary Fig. 1). Finally, 308 obese patients (BMI \geq 30 kg/m²) diagnosed with urinary stone disease were included in the analysis.

2. Measurements and definition of parameters

Predicted BMR was calculated using the Harris–Benedict equation as follows: for men, $66+(13.7\times\text{weight})+(5\times\text{height})-(6.8\times\text{age})$; for women, $655+(9.6\times\text{weight})+(1.8\times\text{height})-(4.7\times\text{age})$ [14].

Urinary metabolic data were available for 182 patients (59.1% of the total cohort), and stone analysis data were available for 227 patients (73.7% of the total cohort). Metabolic evaluation was done at least 4 weeks after the last stone episode. Medications that could affect serum and 24 hours urine chemistry results were discontinued at least 2 weeks before complete metabolic evaluation. Urinary stone risk in urine was evaluated on the basis of the following parameters: sodium (iron selective electrode method), calcium (ocresolphthalein complex), uric acid (uricase colorimetry method), oxalate (oxalate oxidase method), citrate (citrate lyase method), and magnesium (xylydyl blue method). The composition of the stone was determined by Fourier-transform infrared spectrometry (Green Cross, Yongin, Korea).

3. Follow-up protocol

Patients were instructed to follow a general recommended diet (low salt, low animal protein, and high fluid) and none were placed on a low-calcium diet. At the initial follow-up visit, all patients underwent detailed radiologic imaging, including plain films, abdominal ultrasonography, and computerized tomography (CT) scans. It was recommended that patients be followed-up every 6 months. At each visit, all patients underwent radiologic evaluation and any obscure stone was confirmed by a CT scan. Stone recurrence was defined as radiographic appearance of stones that were not present on the previous examination regardless of clinical significance. Time to stone recurrence was the time interval between the preceding examination and the most recent examination at which the new stone was detected.

4. Statistical analysis

Patients were categorized into two BMR categories according to the median BMR value (<1,145 kcal/day or \geq 1,145 kcal/day). Clinical and 24 hours urinary chemistry were compared between groups using Fisher's exact test for

Table 1. Baseline patient characteristics

Parameter	Predicted basal metabolic rate		p-value
	<1,145 kcal/day (n=153)	≥1,145 kcal/day (n=155)	
Age (y)	49.88±13.92	36.08±10.07	<0.001
BMI (kg/m ²)	32.03±4.63	33.84±3.52	<0.001
Sex			0.006
Male	111 (72.5)	89 (57.4)	
Female	42 (27.5)	66 (42.6)	
Hypertension			0.166
Yes	38 (24.8)	28 (18.1)	
No	115 (75.2)	127 (81.9)	
Diabetes mellitus			0.002
Yes	26 (17.0)	9 (5.8)	
No	127 (83.0)	146 (94.2)	
Stone history			0.158
FSF	127 (83.0)	118 (76.1)	
RSF	26 (17.0)	37 (23.9)	
Stone location			0.262
Kidney	26 (17.0)	19 (12.3)	
Ureter	127 (83.0)	136 (87.7)	
Stone composition			0.418
Calcium oxalate	83 (76.1)	98 (83.1)	
Uric acid	24 (22.0)	18 (15.3)	
Calcium phosphate	2 (1.8)	2 (1.7)	
Not available	44	37	

Values are presented as mean±standard deviation, number (%), or number only.

BMI, body mass index; FSF, first stone former; RSF, recurrent stone former.

categorical variables and Student’s t test for continuous variables. The Kaplan-Meier method was used to estimate recurrence-free survival, and differences were assessed using log-rank statistics. Univariate and multivariate survival analyses were performed using the Cox proportional hazard regression model. Differences were considered significant at p<0.05, and all reported p-values were two-sided. Analyses were performed using SPSS 24.0 software (IBM Corp, Armonk, NY, USA).

5. Ethics statement

The study was carried out in agreement with all applicable laws and regulations, good clinical practice, and the ethical principles described in the Declaration of Helsinki. All patients provided written informed consent to participate in the study, and collection and analysis of all samples was approved by the Institutional Review Board of the Chungbuk National University (approval number: 2011-04-004).

Table 2. Correlation between predicted basal metabolic rate and 24 hours urine constituents

Parameter	r ^a	p-value ^b
Calcium (mg/day)	0.158	0.086
Sodium (mEq/day)	0.197	0.031
Uric acid (mg/day)	0.287	0.001
Oxalate (mg/day)	0.097	0.292
Citrate (mg/day)	0.013	0.218
Magnesium (mg/day)	0.031	0.737
Phosphate (g/day)	0.198	0.030

^a:Partial correlation coefficient, adjusted by age, sex, and body mass index. ^b:p-values are based on partial correlation analysis.

RESULTS

1. Comparison of demographic and stone variables according to predicted basal metabolic rate category

The high BMR group was more likely to be younger and female, and to have a high BMI and lower incidence of diabetes than the low BMR group (each p<0.05).

No significant differences were seen with respect to the presence of hypertension, previous stone history, stone location, and stone composition (all p>0.05; Table 1).

2. Association between predicted basal metabolic rate and 24 hours urine constituents

There was a positive correlation between BMR and 24 hours urinary sodium (r=0.197, p=0.031), uric acid (r=0.287, p=0.001), and phosphate (r=0.198, p=0.030) excretion (Table 2).

Regarding urinary stone-forming constituents, subjects with a high BMR had significantly higher levels of calcium (p=0.004) and uric acid (p=0.028) than subjects with a low BMR. There was no significant difference between the two groups with respect to urinary sodium, oxalate, citrate, magnesium, or phosphate excretion (each p>0.05; Table 3).

3. Predicted basal metabolic rate as a predictor of stone recurrence

The 97 patients (31.5% of total cohort) who were followed up for ≥12 months were included in stone recurrence analyses. Kaplan–Meier estimates showed that the high BMR group had a significantly shorter stone recurrence-free period than the low BMR group (log-rank test, p<0.001) (Fig. 1). Multivariate Cox regression analyses identified hypertension (hazard ratio [HR], 2.941; 95% confidence interval [CI], 1.339–6.459; p=0.007) and predicted BMR (HR, 2.759; 95% CI, 1.413–5.386; p=0.003) as independent risk factors for stone recurrence (Table 4).

DISCUSSION

Here, we examined the effect of predicted BMR on 24 hours urinary metabolic profiles and stone recurrence in obese stone patients. The amounts of urinary stone-forming constituents such as calcium and uric acid were significantly

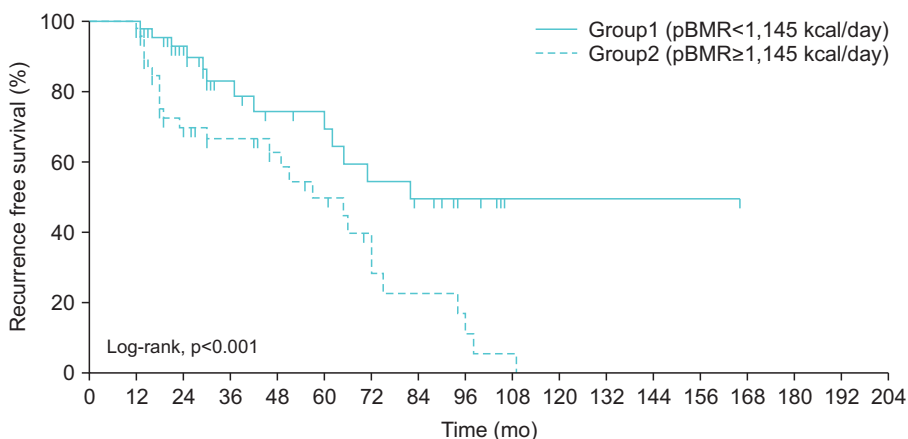
higher in the high BMR group. Importantly, predicted BMR was an independent risk factor for stone recurrence. This finding implies that BMR may be an easily measured parameter to identify individuals at risk for recurrence. Therefore, more aggressive preventive measures should be considered to prevent stone recurrence in obese stone patients with a high BMR.

BMR is defined as the amount of energy required to maintain structural and functional homeostasis at rest under fasting and thermoneutral conditions, and represents up to 60%–70% of total energy expenditure; generally, it is measured by indirect calorimetry [15,16]. BMR is an indicator of overall body metabolism and may be a marker of metabolic health, independent of adiposity [16]. Recent epidemiologic studies show that the incident stone risk increases with BMI [12,13,17]. Obesity increases urinary excretion of promoters of crystallization and urine acidity, and contributes to an increase in calcium oxalate lithogenesis [18-20]. Our previous data show that obesity is associated with metabolic alterations and urinary stone recurrence [21]. Although urolithiasis is considered to be strongly associated with body fatness

Table 3. Comparison of 24 hours urine constituents in stone formers (n=308) according to nutritional status

Parameter	Predicted basal metabolic rate		p-value
	<1,145 kcal/day (n=153)	≥1,145 kcal/day (n=155)	
Calcium (mg/day)	181.10±110.78	239.21±113.64	0.004
Sodium (mEq/day)	224.46±90.33	221.44±99.76	0.859
Uric acid (mg/day)	710.25±261.43	824.89±329.66	0.028
Oxalate (mg/day)	31.09±17.51	35.76±43.49	0.426
Citrate (mg/day)	436.01±299.40	464.77±349.07	0.620
Magnesium (mg/day)	110.81±69.94	107.33±36.08	0.731
Phosphate (g/day)	0.80±0.32	0.89±0.33	0.117

Values are presented as mean±standard deviation. All p-values were calculated using Student's t test.



Number at risk	
Group1:	48 47 30 20 16 14 11 9 5 1 1 1 1 1 0
Group2:	49 45 25 20 15 11 5 4 2 1 0 0 0 0 0

Fig. 1. Kaplan–Meier survival curves of recurrence-free survival, categorized according to predicted basal metabolic rate (pBMR).

Table 4. Multivariate Cox regression analysis of factors predictive of stone recurrence

Variable	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (y)	1.056 (0.998–1.117)	0.057		
Sex (female)	0.858 (0.436–1.688)	0.657		
Stone history (yes)	0.827 (0.343–1.993)	0.672		
BMI (kg/m ²)	1.061 (0.973–1.156)	0.181		
HTN (yes)	2.678 (1.238–5.792)	0.012	2.941 (1.339–6.459)	0.007
DM (yes)	0.423 (0.129–1.388)	0.156		
pBMR (≥1,145 kcal/day)	2.629 (1.350–5.120)	0.004	2.759 (1.413–5.386)	0.003

Multivariate Cox regression analysis was used to estimate odds ratio with the corresponding 95% CI.

HR, hazard ratio; CI, confidence interval; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; pBMR, predicted basal metabolic rate.

or lifestyle habits, there are numerous cases in which urolithiasis develops despite a normal body habitus or healthy lifestyle [22]. We hypothesized that a high BMR, which represents increased overall body metabolism, is associated with unique aberrations in urine physico-chemistry and stone formation. Increased energy metabolism may lead to changes in urinary pH and increased excretion of some urinary stone components. In addition, since BMR incorporates additional informative clinical variables (i.e., age and sex) beyond BMI, it could be used to identify subgroups at greater risk of stone recurrence that would not otherwise have been identified solely by BMI. Although there is still controversy, evidence suggests sex- and age-specific differences in stone incidence, as well as in the composition of urolithiasis [23-25].

Our preliminary analyses revealed that BMR predicts stone recurrence only in obese stone patients. The biological mechanisms explaining why BMR does not affect stone recurrence in underweight, normal, or overweight patients are unknown. Further research is needed to confirm the relationship between BMR and urinary stone risk, and whether these relationships are dependent on body fatness.

This study has several inherent limitations. First, it was retrospective, which means that there may be some sampling bias. Second, urinary metabolic and stone composition data were available for only 59.1% and 73.7%, respectively, of the total cohort. Considering that recurrence analysis was also conducted in a small portion of the cohort (31.5%) and relatively short follow-up duration, increasing the sample size and follow-up duration are recommended. Another issue is that BMR equations do not make a distinction between lean mass and fat mass, which differ metabolically [16]. Predicted BMR using equations may overestimate actual BMR, particularly among overweight and obese individuals. Although indirect calorimetry may be a more reliable tool for measuring BMR, it is expensive and inconvenient; predictive equations serve us better in routine practice [16]. Our findings therefore should be viewed as exploratory and further research is needed to confirm the prognostic value of BMR in patients with urolithiasis.

CONCLUSIONS

The present study highlights the effect of predicted BMR on 24 hours urinary metabolic profiles and stone recurrence in obese stone patients. This finding implies that BMR may be an easily measured parameter to identify individuals at risk for recurrence, and that more aggressive preventive measures should be considered to prevent stone recurrence in obese stone patients with a high BMR.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Ho Won Kang and Sang-Cheol Lee. Data acquisition: Hee Youn Lee and Kyeong Kim. Statistical analysis: Ho Won Kang, Sung Pil Seo, and Won Tae Kim. Data analysis and interpretation: Yun-Sok Ha and Won Tae Kim. Drafting of the manuscript: Ho Won Kang and Sung Pil Seo. Critical revision of the manuscript: Yun-Sok Ha, Yong-June Kim, Wun-Jae Kim, and Sang-Cheol Lee. Supervision: Yong-June Kim, Seok-Joong Yun, Wun-Jae Kim, and Sang-Cheol Lee. Approval of the final manuscript: all authors.

SUPPLEMENTARY MATERIAL

Supplementary material can be found via <https://doi.org/10.4111/icu.20200438>.

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