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Nutritional status assessed by the Controlling Nutritional Status (CONUT) score as a predictor of recurrence of urolithiasis

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Purpose: We aimed to determine the influence of nutritional status on urinary metabolic abnormalities and stone recurrence in patients with urolithiasis.

Materials and Methods: We analyzed data for 464 stone-formers and 464 propensity-score-matched control patients that had been collected between 2003 and 2015. Nutritional status was evaluated by use of the Controlling Nutritional Status (CONUT) score, and patients were placed into two CONUT score categories (0–1 and ≥2). Serum and 24-hour urinary metabolites were evaluated in 464 stone-formers. Kaplan–Meier and multivariate Cox regression analyses were performed to assess the influence of nutritional status on stone recurrence. Stone recurrence was defined as radiographic appearance of new stones during the follow-up period.

Results: Stone-formers showed a higher prevalence of poor nutrition (CONUT score ≥2) than did the propensity-score-matched control patients (p<0.001). Stone-formers who had poor nutritional status had significantly lower 24-hour urinary calcium but higher oxalate excretion (each p<0.05). Kaplan–Meier estimates demonstrated that stone-formers with poor nutritional status also experienced stone recurrence more rapidly (log-rank test, p=0.014). Multivariate Cox regression revealed that poor nutritional status was independently associated with stone recurrence (hazard ratio, 1.736; 95% confidence interval, 1.041–2.896; p=0.034).

Conclusions: The CONUT score, an easily measured immunonutritional biomarker, is independently associated with a higher risk for stone recurrence in patients with urolithiasis. This implies that not only dietary excess, but also undernourished status, may be associated with aberrations in urine physicochemistry and stone recurrence.

Keywords: Nutritional status; Recurrence; Urinary calculus

INTRODUCTION

The lifetime prevalence of urolithiasis is estimated at 1% to 13% and varies by population and geographic location. Importantly, recent epidemiologic studies have demonstrated that the global prevalence has increased over the last sev-

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eral decades [1-3]. In addition, the incidence of recurrence is as high as 30% to 50% within 10 years of the first episode; therefore, appropriate education and preventive measures are considered to be as important as the initial intervention [4,5]. A number of investigators have suggested that features of the metabolic syndrome, such as obesity, hypertension, dyslipidemia, and diabetes, which share the common underlying pathology of visceral fat accumulation and insulin resistance, are associated with urolithiasis [6-9], and numerous studies have shown high prevalences of urolithiasis and its recurrence in people with obesity [10-13]. However, despite this strong association between urolithiasis and obesity, urolithiasis develops independently of obesity in numerous patients. It is our hypothesis that not only dietary excess, but also poor nutrition, may be associated with aberrations in urinary physicochemistry and stone recurrence. However, there have been no clinical studies of the impact of nutritional status on the development of urolithiasis.

Comprehensive nutritional indexes, such as the Controlling Nutritional Status (CONUT) score and the Prognostic Nutritional Index (PNI), have been developed and are widely used to evaluate nutritional status [14,15]. The CONUT score is an easily measured tool for the early detection and ongoing monitoring of nutritional status that is based on serum albumin concentration (an indicator of protein reserves), total cholesterol level (a caloric depletion parameter), and lymphocyte count (an indicator of immune defense) [16]. A decrease in each component is assigned a high score; therefore, a higher score indicates undernourished status. In the present study, we evaluated the relationship of nutritional status, assessed by use of the CONUT score, with aberrations in urinary physicochemistry and risk for stone recurrence in stone-formers.

MATERIALS AND METHODS

1. Characteristics of case and control patients

We retrospectively analyzed detailed clinical data for 3,631 consecutively identified stone-formers who had been diagnosed with urolithiasis between 2003 and 2015. Patients were excluded if they were aged 17 years or younger; had incomplete 24-hour urinary data (24-hour urinary creatinine <17 mg/kg for male and <13 mg/kg for female) or were missing preoperative laboratory results; had impaired renal function (serum creatinine >1.5 mg/dL); had a diagnosis of bladder stones or staghorn calculi; or had urinary tract anomalies (obstruction, malformation of the urologic system) or metabolic disease that could have affected calcium and bone metabolism. Of the 3,631 consecutive patients who were initially considered, data from 464 were included in the final analysis.

Non-stone-formers were recruited from among individuals who visited the Health Promotion Center of Chungbuk National University Hospital for routine checkups during the same period. The health checkup program includes general body measurements (height, body mass index [BMI], and blood pressure), blood laboratory tests (complete blood cell count and chemistry), urinalyses, abdominal ultrasonography, and the completion of a questionnaire regarding the patient's medical history, use of medications, and history of episodes of urolithiasis. Participants who had a history of urolithiasis or for whom a diagnosis was made by abdominal ultrasonography were excluded. The control participants were 1:1 propensity-score-matched with the 464 consecutive first-time stone-formers with respect to age, sex, and body mass index, and in this way 464 participants were selected as the control group.

2. Measurements and definition of parameters

Fasting blood samples were obtained for the measurement of serum albumin, total cholesterol level, and total lymphocyte count from stone-formers and control patients, and CONUT scores were calculated by using these three parameters (Supplementary Table 1). Demographic features and 24-hour urinary metabolic profiles were recorded for stone-formers. Metabolic evaluations were performed at least 4 weeks after the episode of urolithiasis ended. Stone-formers were instructed to follow generally recommended dietary and lifestyle modifications. The composition of stones was determined by using Fourier-transform infrared spectrometry (Green Cross, Yongin, Korea), and these data were available for 280 patients (60.3% of the stone-formers). Stone recurrence was defined as the radiographic detection of new stones that were not present at the previous examination.

3. Statistical analysis

The propensity score method was used to match the case and control groups with respect to key covariates (age, sex, and BMI) by using multivariable logistic regression. Matching for propensity score was performed by using the R package 'matching' tool (https://www.r-project.org/).

The stone-formers were placed into two groups according to their CONUT score: a normal nutritional status group (CONUT score 0–1; n=226, 48.7%) and a poor nutritional status group (CONUT score ≥2; n=238, 51.3%) (Table 1). Clinical and 24-hour urinary chemistry data were compared between the groups. The Kaplan–Meier method was used to estimate recurrence-free survival, and differences were assessed by

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Table 1. Baseline characteristics and nutritional status of non-stone-formers (controls) and stone-formers

Parameter	Controls (n=464)	Stone-formers (n=464)	p-value
Age (y)	51.3±13.5 (20–86)	51.3±13.9 (18–81)	0.973[a]
BMI (kg/m²)	24.9±3.0	24.9±3.6	0.972[a]
Sex			>0.999[c]
Male	298 (64.2)	297 (64.0)	
Female	166 (35.8)	167 (36.0)	
Serum albumin (g/dL)	4.6±0.3	4.4±0.3	<0.001[b]
Total lymphocyte count (/mm³)	2,220.9±650.8	2,115.6±677.0	0.005[b]
Total cholesterol (mg/dL)	188.6±39.0	187.4±40.4	0.823[b]
CONUT score (sum)	0.9±1.1	1.8±0.9	<0.001[b]
Nutritional status			<0.001[c]
Normal (CONUT score 0–1)	366 (78.9)	226 (48.7)	
Poor nutrition (CONUT score ≥2)	98 (21.1)	238 (51.3)	

Values are presented as mean±standard deviation (range) or number (%).
BMI, body mass index; CONUT, Controlling Nutritional Status.
p-values were calculated by using [a]Student's t-test, [b]Mann–Whitney U-test, or [c]Fisher's exact test.

using the log-rank test. Univariate and multivariate survival analyses were conducted by using the Cox proportional hazards regression model. Variables with a p-value less than 0.05 in the univariate analysis were included in the multivariate analysis. Differences were considered significant when p<0.05, and all reported p-values are two-sided. Analyses were performed using SPSS 24.0 software (IBM Corp., Armonk, NY, USA).

4. Ethics statement

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

RESULTS

1. Baseline characteristics of the participants

The baseline characteristics of the 464 stone-formers and 464 control patients are presented in Table 1. The mean age, BMI, and sex distribution did not differ significantly between the control patients and the stone-formers (Table 1).

2. Nutritional status of the stone-formers and control patients

The mean serum albumin concentration and lymphocyte count were significantly higher in the control patients than in the stone-formers (p<0.001 and p=0.005, respectively), but there was no significant difference in serum total cholesterol concentrations between the two groups (p=0.823). The mean CONUT score and the prevalence of dyslipidemia differed significantly between the groups (each p<0.001) (Table 1).

3. Relations of nutritional status with clinical and metabolic features in stone-formers

Stone-formers with poor nutritional status (CONUT score ≥2) tended to be older and were more likely to have diabetes or hypertension than were stone-formers with normal nutritional status (CONUT score 0–1) (each p<0.05). The sex distribution, BMI, stone location, stone composition, and primary treatment modality did not differ significantly between the groups (each p>0.05) (Table 2).

Regarding their 24-hour urinary chemistry, stone-formers with a high CONUT score had significantly lower urinary calcium excretion than did stone-formers with normal nutritional status (p=0.004), but urinary oxalate excretion was significantly higher in the poor nutritional status group than in the normal nutritional status group (p<0.001) (Table 3).

There was no significant difference in the CONUT score between the subgroups of patients in whom stone composition was known (p=0.135; Supplementary Table 2).

4. Nutritional status and stone recurrence

The 268 patients (57.8% of total stone-formers) who were followed for >6 months were included in the analyses of recurrence. The median follow-up period was 15 months (interquartile range, 8–27 months). With regard to 24-hour urinary metabolic profiles, there was no significant difference between stone-formers who demonstrated recurrence and

Table 2. Baseline characteristics of stone-formers, according to nutritional status

Parameter	Nutritional status		p-value
	Normal (CONUT score 0–1)	Poor nutrition (CONUT score ≥2)	
Number of patients	226 (48.7)	238 (51.3)	
Age (y)	49.8±12.2 (19–75)	52.8±15.2 (18–81)	0.021[a]
BMI (kg/m^2)	25.0±3.4	24.8±3.8	0.599[a]
Sex			0.209[c]
Male	138 (61.1)	159 (66.8)	
Female	88 (38.9)	79 (33.2)	
Family history	55 (24.3)	46 (19.3)	0.216[c]
HTN	41 (18.1)	93 (39.1)	<0.001[c]
DM	16 (7.1)	58 (24.4)	<0.001[c]
Stone location			0.211[c]
Kidney	42 (18.6)	56 (23.5)	
Ureter	184 (81.4)	182 (76.5)	
Stone composition			0.162[b]
Calcium oxalate	89 (70.6)	100 (64.9)	
Uric acid	21 (16.7)	40 (26.0)	
Calcium phosphate	5 (4.0)	2 (1.3)	
Mixed stone	11 (8.7)	12 (7.8)	
Unknown	100	84	
Primary treatment			0.245[b]
Observation or MET	99 (43.8)	90 (37.8)	
ESWL	23 (10.2)	20 (8.4)	
Surgery	104 (46.0)	128 (53.8)	

Values are presented as number (%) or mean±standard deviation (range).
BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; MET, medical expulsive therapy; ESWL, extracorporeal shock wave lithotripsy.
p-values were calculated by using [a]Student's t-test, [b]chi-squared test, or [c]Fisher's exact test.

Table 3. Comparison of 24-hour urinary constituents in stone-formers, according to nutritional status

Parameter	Nutritional status		p-value
	Normal (CONUT score 0–1)	Poor nutrition (CONUT score ≥2)	
Number of patients	226 (48.7)	238 (51.3)	
Calcium (mg/day)	181.95±91.77	162.33±104.35	0.004
Sodium (mEq/day)	163.77±64.29	163.25±72.19	0.624
Uric acid (mg/day)	591.44±226.59	592.49±238.49	0.832
Oxalate (mg/day)	28.70±15.13	34.71±29.14	<0.001
Citrate (mg/day)	422.99±287.18	401.94±262.61	0.399

Values are presented as number (%) or mean±standard deviation.
CONUT, Controlling Nutritional Status.
p-values were calculated by using Mann–Whitney U-test.

those who did not (each p>0.005; Supplementary Table 3).

Kaplan–Meier estimates demonstrated that participants with poor nutritional status experienced stone recurrence faster than did those with normal nutritional status (log-rank test, p=0.014) (Fig. 1). Multivariate Cox regression analysis revealed that poor nutritional status was independently associated with stone recurrence (hazard ratio, 1.736; 95% confidence interval, 1.041–2.896; p=0.034) (Table 4).

DISCUSSION

In the present study, we assessed the influence of nutritional status on urinary metabolic abnormalities and stone recurrence in patients with urolithiasis. Our data show that poor nutritional status is closely related to both stone formation and stone recurrence. This finding implies that not only dietary excess but also poor nutritional status may induce aberrations in urinary physicochemistry and stone recurrence. A higher CONUT score may be an indicator of a metabolic phenotype that is associated with a higher risk for stone recurrence and may be a useful indicator of adequate nutritional status, independent of adiposity.

Dietary and lifestyle modifications represent the most effective and least expensive measures for stone prevention. A general dietary and lifestyle modification includes a sufficient fluid intake, increased intake of fruits and vegetables, reduced intake of meats and animal fats, restricted intake of oxalate-rich foods, a high citrate intake, adequate dietary

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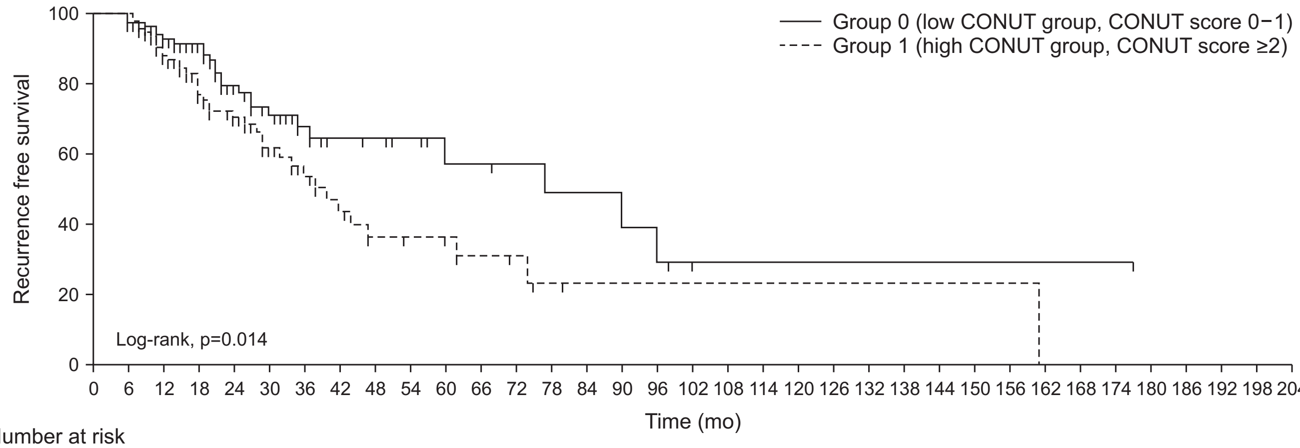

Number at risk

Group	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96	102	108	114	120	126	132	138	144	150	156	162	168	174	180
Group: 0	120	111	73	59	40	31	20	14	13	11	8	8	7	5	5	4	3	1	1	1	1	1	1	1	1	1	1	1	1	1	0
Group: 1	148	140	75	50	37	26	18	13	9	8	7	5	4	2	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0

Fig. 1. Kaplan–Meier curves of recurrence-free survival according to nutritional status in stone-formers. CONUT, Controlling Nutritional Status.

Table 4. Multivariate Cox regression analysis for the prediction of stone recurrence

Variable	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (y)	1.013 (0.993–1.033)	0.205	-	-
Sex (female)	0.540 (0.314–0.931)	0.026	0.672 (0.386–1.170)	0.160
Family history (yes)	0.598 (0.660–2.060)	0.598	-	-
BMI (kg/m^2)	1.081 (1.003–1.165)	0.042	1.060 (0.981–1.145)	0.138
HTN (yes)	1.561 (0.952–2.558)	0.077	-	-
DM (yes)	0.951 (0.497–1.822)	0.880	-	-
24-hr urinary calcium (mg/day)	0.999 (0.996–1.002)	0.423	-	-
24-hr urinary sodium (mEq/day)	1.000 (0.996–1.003)	0.934	-	-
24-hr urinary uric acid (mg/day)	0.999 (0.998–1.000)	0.149	-	-
24-hr urinary oxalate (mg/day)	1.005 (0.999–1.010)	0.095	-	-
24-hr urinary citrate (mg/day)	1.000 (0.999–1.000)	0.349	-	-
Poor nutritional status (CONUT score ≥2)	1.850 (1.120–3.054)	0.016	1.736 (1.041–2.896)	0.034

HR, hazard ratio; CI, confidence interval; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; CONUT, Controlling Nutritional Status.
Multivariate Cox regression analysis was used to estimate the HR and the corresponding 95% CI.

calcium intake, reduced salt intake, regular physical activity, and body weight control [17,18]. Excess food intake increases the traffic of lithogenic substances, such as calcium, uric acid, and oxalate [11]. Obesity has been shown to be associated with lower urinary pH and higher urinary excretion of sodium, uric acid, and calcium and contributes to the development of urolithiasis [12,19-24]. A study by Lee et al. [10] revealed a significant association between obesity and urinary biochemical abnormalities, as well as stone recurrence-free survival. Those authors suggested that weight control may be considered as one means of reducing the risk for stone recurrence [10]. However, there are no epidemiologic studies to date demonstrating the benefits of weight loss, despite the strong evidence of a link between obesity and urolithiasis. Indeed, bariatric surgery is frequently associated with hyperoxaluria and stone formation, and the commonly used low-carbohydrate diets increase the risk for formation of both calcium and uric acid stones [11]. Another problem in clinical practice is that there are numerous cases in which urolithiasis develops independent of obesity [13]. Therefore, we hypothesized that not only dietary excess but also poor nutritional status may induce aberrations in urinary physicochemistry and stone recurrence.

In the present study, we first assessed the CONUT score in patients with urolithiasis to determine the influence of nutritional status on urinary metabolic abnormalities and stone recurrence. Stone-formers showed a higher prevalence of poor nutritional status than did propensity-score-matched control patients. Nutritional status has been shown to be associated with 24-hour urinary chemistry, such as calcium and oxalate excretion. Although mean values of calcium and oxalate urinary excretion were within normal limits, stone-formers with a high CONUT score had a significantly higher prevalence of hyperoxaluria than did stone-formers with normal nutritional status (24.4% vs. 15.5%, p=0.020, data not shown). In contrast, the prevalence of hypercalciuria between the two groups did not achieve statistical significance (16.4% vs. 21.2%, p=0.192, data not shown). These findings may implicate hyperoxaluria as the major lithogenic risk factor in stone-formers with poor nutritional status. In addition, we have shown that nutritional status, assessed by using the CONUT score, is independently associated with a higher risk for stone recurrence in patients with urolithiasis. Poor nutritional status was also associated with lower urinary excretion of calcium but higher urinary oxalate excretion. The serum concentration of albumin, a marker of protein-energy malnutrition, is paradoxically lower in stone-formers than in patients without urolithiasis. Because the consumption of animal protein contributes to hyperuricosuria, a restriction of animal protein consumption is recommended for patients with urolithiasis [25,26]. The present findings should not be interpreted as evidence contrary to general recommendations regarding reduced animal protein intake for stone prevention. Instead, our results highlight the practical value of assessing nutritional status with the CONUT score to tailor patient diet education programs and the development of medical weight loss programs.

There are several limitations to this study. First, the present study is limited by biases inherent to its retrospective design. Relatively short periods of follow-up also warrant consideration. To minimize selection bias, we used the propensity score method. In addition, patients with staghorn calculi were excluded to minimize the potential confounding bias by urinary tract infection. Risk factors predisposing to staghorn stone formation include urinary tract obstruction, long-term use of an indwelling urethral catheter, and neurogenic bladder pathology [27]. Older adults with comorbidities, malnourishment, or immobilization are more prone to developing urinary tract infections by urease-producing bacteria, which subsequently facilitates the formation of staghorn stones. Therefore, the CONUT score may also be a valuable tool for identifying the risk of developing staghorn stones in older malnourished patients. In the present study, staghorn calculi were not considered in a subgroup analysis. Further collaborative research is needed to reveal the relationship between nutritional status and the risk of developing staghorn stones.

CONCLUSIONS

The CONUT score, which is an easily calculated immunonutritional biomarker, is independently associated with a higher risk for stone recurrence in patients with urolithiasis. This finding implies that not only dietary excess but also undernourished status may induce aberrations in urinary physicochemistry and stone recurrence. The present findings highlight the practical value of assessing nutritional status by use of the CONUT score for the tailoring of diet education programs and the development of medical weight loss programs for patients with urolithiasis.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Hee Youn Lee and Sang-Cheol Lee. Data acquisition: Hee Youn Lee and Kyeong Kim. Statistical analysis: Ho Won Kang, Hee Youn Lee, and Won Tae Kim. Data analysis and interpretation: Yun-Sok Ha and Won Tae Kim. Drafting of the manuscript: Ho Won Kang and Hee Youn Lee. 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 MATERIALS

Supplementary materials can be found via https://doi.org/10.4111/icu.20210031.

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