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Original Article

Clinical and demographic factors associated with compliance and subsequent urinary metabolic changes in first-time ureteral stone formers

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Dietary and lifestyle modifications are widely prescribed to prevent recurrence of urolithiasis, although little is known about the clinical and demographic factors associated with patient compliance and urinary metabolic changes. The present study assessed the clinical and demographic factors influencing compliance with a modified diet and lifestyle in first-time ureteric stone formers as well as determined the effects of compliance on urinary stone risk factors. We retrospectively reviewed the medical records of 53 patients presenting with ureteric calcium stones. Using a self-completed questionnaire, patients were classified according to compliance with seven recommendations for modifying diet and lifestyle into good compliance group (complied with ≥ three recommendations) and poor compliance group. Before (on a random diet) and after prescribing the modifications, 24 hour urine samples were collected from those in the good and poor compliance group. The stone size at presentation and initial treatment modality were closely associated with patient compliance (*P*=0.019, *P*=0.027, respectively). Citrate excretion significantly increased in the good compliance group after adopting modifications (*P*=0.012), whereas the poor compliance group did not show a statistically significant difference. Moreover, patients in the poor compliance group showed significantly increased urinary calcium excretion by the end of the study (*P*=0.040). After adjustments for age, sex, body mass index, and metabolic abnormality status, poor compliance was found to be an independent risk factor for persistence or development of hypocitraturia (OR: 3.885; 95% CI: 1.102~13.694; *P*=0.035). In conclusion, our results imply that patient education programs regarding diet and lifestyle should be tailored to the individual's clinical and demographic characteristics.

Key words: urinary calculi, recurrence, compliance, diet, hypocitraturia

Introduction

Urolithiasis is a common urological disease with a reported rate of stone recurrence between 30 to 50% upon mean follow-up of 2~7.1 years [1-3]. Thus, prevention of stone recurrence has become important. Dietary and lifestyle modifications are widely prescribed to prevent recurrence of urolithiasis [4-6], with increased fluid intake (≥2 L/day), reduced animal protein intake, reduced salt intake, increased fruit and vegetable intake (particularly those rich in potassium), restricted intake of oxalate-rich foods, adequate dietary calcium intake, and adequate physical exercise and body weight control being the general recommendations. Although well-designed randomized trials have been carried out to test the effects of modifying intake of individual dietary factors [7-11], the comprehensive effect of general dietary and lifestyle changes on prevention of stone recurrence has not been examined. Moreover, patient compliance with such modifications may be crucial to stone prevention, but little is known about the clinical and demographic factors associated with compliance.

In this study, we assessed the clinical and demographic factors influencing compliance with a modified diet and lifestyle in first-time ureteral stone formers. We also determined the effects of compliance on risk factors associated with urinary stone formation.

Materials and Methods

Patient characteristics and data collection

The medical records of 316 patients who presented with ureteric calculi between January 2011 and December 2012 were retrospectively reviewed. Patients were excluded if they had a recurrent stone episode, non-calcium-containing stones, or metabolic disease that could affect calcium metabolism. Subjects were eligible if they

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had two sequential 24 hr urine samples available; one collected while on a random diet at presentation and one collected six months after prescription of seven dietary and lifestyle modifications (increased fluid intake (≥2 L/day), reduced animal protein intake, reduced salt intake, increased fruit and vegetable intake (particularly those rich in potassium), restricted oxalate-rich food intake, adequate dietary calcium intake, and physical exercise and body weight control). During the last visit, subjects completed a self-assessed questionnaire about compliance with each of the seven recommendations over the previous 6 months. Fifty-three patients satisfied the selection criteria and were categorized into two groups according to rate of compliance with the recommendations as follows: good compliance group (complied with three or more recommendations) and poor compliance group (complied with fewer than three recommendations).

Clinical and demographic factors such as gender, age, body mass index (BMI), medical history, radiologic finding of initial presenting stone, and initial treatment modality were analyzed for association with patient compliance.

All patients and controls provided written informed consent to participate in the study, and collection and analysis of all samples were approved by the Institutional Review Board of Chungbuk National University (IRB number: 2011-04-004).

Measurement and definition of parameters

Risk of forming urinary stones was evaluated from measurements of the following parameters in urine: sodium (ion-selective electrode method), calcium (o-cresolphthalein complexone method), uric acid (uricase colorimetric method), oxalate (oxalate oxidase method), citrate (citrate lyase method), and magnesium (xylidyl blue method). Urinary metabolic abnormalities were classified using the definitions of Lifshitz *et al* and Norman [12, 13].

Statistical analysis

The continuous variables are expressed as means ± standard deviation (S.D.). Association of clinical parameters with patient compliance was determined by comparing each parameter in the good and poor compliance groups using the chi-square or Fisher's exact test and the Mann-Whitney U test. Changes in urine volume and levels of constituents after prescription of the modified diet and lifestyle were assessed by the Wilcoxon signed-rank test. Multivariate regression analyses were used to determine the impact of patient compliance on urinary stone risk factors. All statistical analyses were performed using SPSS software version 21.0, and all were performed with two-tailed tests. $P<0.05$ was considered statistically significant.

Results

Baseline characteristics

The baseline characteristics of the 53 patients selected for study are presented in Table 1. The mean age was 41.1 years (range, 20~70 years), and 36% were men. Mean stone size at presentation was 5.86 mm, and stones were located in the upper ureter of 27 patients (50.9%), in the mid ureter of 12 patients (22.6%), and in the lower ureter of 14 patients (26.4%). Twenty patients (37.7%) were treated with extracorporeal shock wave lithotripsy and 12 (22.6%) with ureteroscopic lithotripsy. The remaining 21 patients (39.6%) chose expectant management as the initial treatment for their ureteral stone, and this group showed a 100% stone clearance rate and mean time to stone clearance of 8.32 days (range, 4~33 days).

Patient compliance with diet and lifestyle modification

During the last visit, patients completed a questionnaire about their compliance with the seven recommendations for modifying their diet and lifestyle over the previous 6 months. Of the 53 patients, 38 (72%) adhered to the recommended fluid intake of at least 2 L/day, 34

Table 1. Baseline characteristics

Parameters	Total cohort (n=53)
Age (years) mean ± S.D. (range)	41.11 ± 11.23 (20~70)
BMI (kg/m^2) mean ± S.D.	24.10 ± 2.85
Obesity (BMI>25)	19 (35.8%)
Gender	
Male	36 (67.9%)
Female	17 (32.1%)
Family history of stones	11 (20.8%)
DM	17 (32.1%)
HTN	9 (17.0%)
Initial stone size (mm) mean ± S.D.	5.86 ± 2.04
Location	
Upper ureter	27 (50.9%)
Mid ureter	12 (22.6%)
Lower ureter	14 (26.4%)
Treatment modality	
Expectant management	21 (39.6%)
ESWL	20 (37.7%)
URS	12 (22.6%)

SD; standard deviation, BMI; body mass index, DM; diabetes mellitus, HTN; hypertension, ESWL; extracorporeal shock wave lithotripsy, URS; Ureterorenoscopic lithotripsy.

(64.2%) increased their intake of fruit and vegetables, 27 (50.9%) reduced salt intake, 23 (43.4%) reduced animal protein intake, and 16 (30.2%) restricted their intake of oxalate-rich foods. Eighteen patients (34.0%) modified their lifestyle to include adequate physical exercise and body weight control (Table 2). Patients were categorized according to their rate of compliance into a good compliance group (compliance with three or more recommendations; n=28) and poor compliance group (complied with fewer than three recommendations; n=25).

Demographic and clinical factors are associated with patient compliance

The two compliance groups did not differ significantly in terms of mean age, gender, BMI, family history of urinary stones, presence of diabetes, or hypertension. Al-

Table 2. Patient compliance with dietary and lifestyle modifications

Parameters	Recommendation	Rates of compliance among the total cohort (%)
Fluid	Increase fluid intake (≥ 2 L/day)	38 (71.7)
Diet	Reduce animal protein intake	23 (43.4)
	Reduce salt intake	34 (64.2)
	Increase intake of fruit and vegetables (rich in potassium)	27 (50.9)
	Restriction of oxalate-rich foods	16 (30.2)
	Adequate dietary calcium intake	11 (20.8)
Lifestyle	Adequate physical exercise and body weight control	18 (34.0)

Table 3. Demographic and clinical factors influencing patient compliance with dietary and lifestyle modifications

Parameters	Good compliance (n=28)	Poor compliance (n=25)	*P*-value
Clinical variables			
Age (years) mean ± S.D.	43.64 ± 11.06	38.28 ± 10.93	0.082†
BMI (kg/m^2)	24.43 ± 3.14	23.72 ± 2.49	0.360†
Gender			1.000*
Male	19 (67.9%)	17 (68.0%)	
Female	9 (32.1%)	8 (32.0%)	
Familial stone history	8 (28.6%)	3 (12.0%)	0.183*
DM	3 (10.7%)	6 (24.0%)	0.278*
HTN	9 (32.1%)	8 (32.0%)	1.000*
Stone-related variables			
Initial stone size (mm) mean ± S.D.	6.54 ± 1.67	5.12 ± 2.19	0.019†
Location			0.926*
Upper ureter	14 (50%)	13 (52%)	
Mid ureter	6 (21.4%)	6 (24%)	
Lower ureter	8 (28.6%)	6 (24%)	
Treatment modality			0.042‡
Expectant management	7 (25%)	14 (56%)	
ESWL	13 (46.4%)	7 (28%)	
URS	8 (28.6%)	4 (16%)	

P-values were based on the *chi-square or Fisher's exact test, †Mann-Whitney U test and ‡linear-by-linear association test.
SD; standard deviation, BMI; body mass index, DM; diabetes mellitus, HTN; hypertension, ESWL; extracorporeal shock wave lithotripsy, URS; Ureterorenoscopic lithotripsy.

though the poor compliance group was of a younger age (38.28 ± 10.93 vs. 43.64 ± 11.06 years), this difference was not statistically significant (*P*=0.082). The ureteric stones found in patients in the poor compliance group at presentation were significantly smaller than those in the good compliance group (5.12 ± 2.19 vs. 6.54 ± 1.67 mm, *P*=0.019), although the location of the initial stone was not significantly different between the two groups (*P*=0.926). In addition, patients in the poor compliance group were more likely to have been managed expectantly than those in the good compliance group (56% vs. 25%, *P*=0.027) (Table 3).

Subsequent metabolic changes according to patient compliance

To investigate metabolic changes resulting from dietary and lifestyle modifications, we compared 24 hr urine stone-forming metabolites before (on a random diet) and after prescribing the modifications from those in the good and poor compliance group. Citrate excretion was significantly higher in the good compliance group (330.35 ± 197.88 mg/day on random diet, vs. 402.25 ± 177.72 mg/day after modifications, *P*=0.012), whereas there was no significant difference in the poor compliance group (311.70 ± 240.98 vs. 323.32 ± 234.55 mg/day, *P*=0.925). Urinary calcium excretion was significantly higher in the sample collected at the end of the study in the poor compliance group (200.21 ± 96.78 vs. 255.08 ± 106.25 mg/day, *P*=0.040) (Table 4).

When adjusted for age, sex, BMI, and other metabolic abnormalities, poor compliance was a risk factor for persistence or development of hypocitraturia (odds ratio: 3.885, 95% confidence interval: 1.102~13.694, *P*=0.035) (Table 5).

Discussion

Our results demonstrate that stone size at presentation as well as initial treatment modality were closely associated with patient compliance. Further, poor patient compliance was found to result in subsequent metabolic derangement. The present study provides important information that can be used to establish a diet and lifestyle education plan for patients with urolithiasis.

Urolithiasis is common and becoming more prevalent in the US and other countries. With recurrence rates as high as 30~50% at 5 years after clearance of the initial stone [14], there is no doubt that preventing recurrence is as important as treating stones when they first appear [15]. Individualized metabolic investigation, dietary recommendations, and medical treatment should all be offered to prevent or reduce recurrence of stone formation [16, 17].

Recommendations regarding fluid intake, diet, and lifestyle have been widely prescribed for the prevention of stone recurrence [14, 16, 18]. Adequate fluid intake is

Table 4. Sequential analysis of 24 hrs urinary constituents according to patient compliance

Parameters	Random diet	After modification	*P*-value*
Good compliance (n=28)			
24 hrs urinary constituents	Mean ± S.D.	Mean ± S.D.	
Calcium (mg)	231.30 ± 89.85	221.08 ± 85.95	0.535
Sodium (mg)	206.69 ± 78.25	230.58 ± 89.17	0.159
Uric acid (mg)	630.10 ± 185.21	616.35 ± 168.72	0.480
Oxalate (mg)	31.94 ± 23.98	26.17 ± 12.47	0.304
Citrate (mg)	330.35 ± 197.88	402.25 ± 177.72	0.012
Urine volume (mL)	1,880.36 ± 723.54	1,898.04 ± 642.09	0.279
Poor compliance (n=25)			
24 hrs urinary constituents	Mean ± S.D.	Mean ± S.D.	
Calcium (mg)	200.21 ± 96.78	255.08 ± 106.25	0.040
Sodium (mg)	199.08 ± 94.90	223.12 ± 83.14	0.271
Uric acid (mg)	581.60 ± 173.53	606.58 ± 171.97	0.476
Oxalate (mg)	29.36 ± 18.35	30.52 ± 20.30	0.968
Citrate (mg)	311.70 ± 240.98	323.32 ± 234.55	0.925
Urine volume (mL)	1,731.60 ± 673.46	1,789.60 ± 627.27	0.721

P-values were based on the *Wilcoxon signed-rank test.

needed to dilute the urine and hence lower the concentrations of lithogenic substances [15]. Large prospective epidemiological studies suggest that a diet with adequate calcium is associated with reduced risk of stone formation [9]. Although there have been no studies demonstrating that restriction of oxalate intake can effectively reduce recurrence of stones, avoidance of high-oxalate foods and vitamin C supplements has been recommended for calcium stone formers with hyperoxaluria [14, 19]. High sodium intake followed by a decrease in proximal sodium reabsorption reduces renal tubular calcium reabsorption [20], and high intake of animal protein contributes to hyperuricosuria, hyperoxaluria, hypocitraturia, and hypercalciuria [21]. Low potassium intake may increase the relative risk of stone formation due to increased urinary calcium and decreased urinary citrate levels [7]. Recent studies have revealed that obesity is associated with changes in serum and urinary chemistry as well as increased recurrent stone formation. Thus, weight control has been recommended as a preventive measure against recurrence of stone formation [22, 23]. As mentioned above, previous studies in the field of diet and urinary stone disease have mainly focused on individual factors. Therefore, there is an urgent need to understand the preventative effects of comprehensive modification of diet and lifestyle on stone recurrence. In addition, to date, there are few data concerning the clinical and demographic factors associated with patient compliance with prescribed modifications. In the current study, we found that stone size at presentation as well as the initial treatment modality were closely associated with patient compliance. Patients in the poor compliance group were more likely to have smaller stones and to have been managed expectantly. More importantly, patient compliance showed a significant influence on subsequent urinary metabolic changes. Patients in the good compliance group showed significantly increased urinary citrate excretion after adopting the modifications, whereas the poor compliance group did not show a significant difference. Moreover, after adjustments for age, sex, BMI, and other metabolic abnormalities, poor compliance was found to be a significant risk factor for persistence or development of hypocitraturia. Numerous studies have shown that low urinary citrate can cause calcium stone formation [24, 25]. Specifically, citrate forms complexes with calcium and thus decreases the amount of ionic calcium available for stone formation [26]. In addition, citrate directly inhibits calcium oxalate nucleation [27]. Furthermore, the poor compliance group showed increased urinary calcium excretion even after diet and lifestyle modifications. These results highlight the practical value of patient compliance with general dietary and lifestyle modifications for the prevention of stone formation.

This study was possibly limited by its retrospective design, which may have introduced sampling bias. Furthermore, it was based on a relatively small sample size and relied on a self-assessment questionnaire. Therefore, to validate our findings, a large prospective study is now required.

Conclusions

This study highlights the practical value of patient compliance with dietary and lifestyle modifications for the prevention of stone formation. The stone size at presentation and initial treatment modality were closely associated with patient compliance. Patient compliance had a significant influence on subsequent urinary metabolic changes. Therefore, it is important to tailor patient education programs according to clinical and demographic characteristics.

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Table 5. Impact of poor compliance on persistence or development of metabolic abnormalities

Parameters	OR*	CI	*P*-value
Hypercalciuria	2.425	0.529~11.122	0.254
Hypernatriuria	0.932	0.225~3.862	0.923
Hyperuricosuria	1.585	0.335~7.493	0.561
Hyperoxaluria	2.254	0.462~10.988	0.315
Hypocitraturia	3.885	1.102~13.694	0.035
Hypovolemia	1.017	0.233~4.648	0.982

*Adjusted for age, sex, BMI and other metabolic abnormalities.
OR; odds ratio, CI; 95% confidence interval.

ment Administration, Republic of Korea.

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