

Evaluation of risk factors for recurrent renal stone formation among Saudi Arabian patients: Comparison with first renal stone episode

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Summary *Objectives: We evaluated the baseline characteristics, and risk factors of renal stone recurrence among Saudi Arabian patients after successful primary stone treatment.*

Materials and methods: In this cross-sectional comparative study, we reviewed the medical records of patients who presented consecutively with a first renal stone episode from 2015 to 2021 and were followed-up by mail questionnaire, telephone interviews, and/or outpatient clinic visit. We included patients who achieved stone-free status after primary treatment. Patients were divided into two groups: group I (patients with first episode renal stone) and group II (patients who developed renal stone recurrence). The study outcomes were to compare the demographics of both groups and to evaluate the risk factors of renal stone recurrence after successful primary treatment. We used Student's t-test, Mann Whitney test or chi-square (χ^2) to compare variables between groups. Cox regression analyses were used to examine the predictors.

Results: We investigated 1260 participants (820 males and 440 females). Of this number, 877 (69.6%) didn't develop renal stone recurrence and 383 (30.4%) had recurrence. Primary treatments were percutaneous nephrolithotomy (PCNL), retrograde intrarenal surgery (RIRS), extracorporeal shock wave lithotripsy (ESWL), surgery and medical treatment in 22.5%, 34.7%, 26.5%, 10.3%, and 6%, respectively. After primary treatment, 970 (77%) and 1011 (80.2%) of patients didn't have either stone chemical analysis or metabolic work-up, respectively.

Multivariate logistic regression analysis revealed that male gender (OR: 1.686; 95% CI, 1.216-2.337), hypertension (OR: 2.342; 95% CI, 1.439-3.812), primary hyperparathyroidism (OR: 2.806; 95% CI, 1.510-5.215), low fluid intake (OR: 28.398; 95% CI, 18.158-44.403) and high daily protein intake (OR: 10.058; 95% CI, 6.400-15.807) were predictors of renal stone recurrence.

Conclusions: Male gender, hypertension, primary hyperparathyroidism, low fluid intake and high daily protein intake increase the risk of renal stone recurrence among Saudi Arabian patients.

KEY WORDS: Renal stone; Risk factors; Recurrence; Saudi Arabia.

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INTRODUCTION

Worldwide, nephrolithiasis is one of the commonest urologic diseases. In the last decades, the prevalence of nephrolithiasis has changed, with prevalence ranges from 7% to 13%, 5% to 9%, and 1% to 5% in North America, Europe, and Asia, respectively (1). The wide prevalence ranges among countries reflect several multifactorial conditions including age, sex, race, climate, occupation, dietary habits, fluid intake, genetic and metabolic diseases (2).

In Asia, the prevalence and incidence of urolithiasis have increased in most of the countries specifically more in the south Asian countries than in the north Asian countries (5.5% to 11.6% compared to 2.6% to 7.2%, respectively) (3). This is because of the higher temperature and excessive sunshine exposure in the south countries than that in the north countries. Saudi Arabia is located in the west Asian region and due to its high temperature and semi-arid climate the prevalence of urinary tract stones was documented to be rising. During the period from 1989 through 2008, the prevalence rate of urolithiasis has been increased from 6.8% (4) to 19.1% (5).

Renal stone recurrence is a devastating health problem, which affects the patients' health-related quality of life (6), as well as represents an extra economic burden for its management (7). In a prospective study, Trinchieri *et al.* studied the stone recurrence rate and risk after a first stone episode and found that 27% of patients developed symptomatic stone recurrence at mean follow-up of 7.5 years. In addition, age at onset of the disease was significantly lower for patients with ≥ 2 recurrence than those who had only 1 or no recurrence (8). Among Asian countries, the reported recurrence rate of urolithiasis in the first year was about 6% to 17%, and at 5 years reaching up to 53%, while the lifetime risk of urinary stones recurrence is estimated to be 60% to 80% (9). In Saudi Arabia, Abdel-Halim *et al.* reported a recurrence rate of renal stone ranging from 38.6% to 53.2% (4).

Studies evaluating the risk factors of renal stone recurrence are not common. Our study aimed to explore the demographic characteristics of primary renal stones for-

mer, as well as the risk factors of renal stone recurrence after successful primary treatment in Saudi Arabia. We believe that the results of this study may provide an insight into ways that can help us to prevent the recurrence of renal stones.

MATERIALS AND METHODS

Study design and ethical statement

A prospective cross-sectional comparative study was carried out at four Saudi Arabia's tertiary centers in Riyadh, Taif and Sharurah cities. The study was approved by the institutional review boards and ethical committee of Princess Nourah bint Abdulrahman University and was performed in accordance with the ethical standards and the Helsinki declaration (*Institutional review board "IRB" registration number: H-01-R-059*). All patients included in our study signed a written informed consent.

We reviewed the medical records of patients who presented consecutively with a first renal stone episode from 2015 to 2021 at urology departments of the participating centers. From March 2020 through March 2021, patients were interviewed either during their follow-up visits in the clinic or by telephone interviews to fill out a questionnaire. A total of 1260 patients completed the questionnaires successfully. Patients were divided into two groups: group I (patients with first episode renal stone) and group II (patients who developed renal stone recurrence).

Inclusion and exclusion criteria

Patients aged ≥ 18 years old with history of successful primary renal stone treatments (i.e., medical or surgical) were included in the current study. We excluded patients with remaining stones after the initial stone episode, patient who had urinary tract malformation, urinary tract obstructive disease, history of pyeloplasty or ureteric reimplantation surgery, renal failure, chronic gastric diseases, and incomplete questionnaire data.

Patients' characteristics

Demographic and baseline patients' characteristics were retrieved from our database including age, gender, *body mass index* (BMI), medical comorbidities such as *diabetes mellitus* (DM), *hypertension* (HTN), cardiac diseases...etc, city of residency, nationality, family history of urolithiasis, and history of recurrent *urinary tract infection* (UTI). Moreover, data regarding renal stone were gathered such as primary or recurrent renal stone, time to first recurrence, frequency of recurrence, previous treatment methods (either surgical or medical), chemical analysis of the stone, and routine metabolic work-up after successful primary treatment.

Follow-up

All patients were followed-up after treatment at 6 weeks, 3 months then yearly until the last visit. Routine postoperative imaging study included *Kidney-Ureter-Bladder* (KUB) X-ray, *urinary ultrasound* (UUS), or *computed tomography* (CT) scan that were performed according to the surgeon preference and/or stone radiopacity. Stone-free status was defined as non-obstructing residual stone

fragments of ≤ 2 mm in size detected at 3 months post-operatively on postoperative imaging studies (10). Recurrent renal stone was defined as new stone formation and/or stone growth during routine follow-up that was diagnosed radiologically (11).

Patients' lifestyle information regarding the level of physical activity per week and dietary habits were obtained through asking the patients to complete a previously published (12, 13) non-validated self-administered questionnaire including selected items (1 question for physical activity and 5 questions for dietary habit). Questionnaires were disseminated among patients either in the clinic during follow up visits and/or through telephone calls. The commonest dietary habits that are associated with increased risk of stone formation and recurrence include; low fluid intake (< 1 liter/day), high salt diet (> 10 g/day), high protein intake (> 100 g/day), low-calcium diet (≤ 400 mg/day), and high intake of oxalate containing foods (14).

Outcome measurement

The primary outcome was to compare groups in order to evaluate the predictors of renal stone recurrence after successful primary treatment. The secondary outcome was to assess demographic characteristics of stone formers in Saudi Arabia.

Statistical analysis

Continuous variables were illustrated as mean \pm standard deviation (SD) or median and *interquartile range* (IQR), whereas categorical variables were illustrated as frequency and percentages (%). To compare variables of group I and group II, we used the Student's t-test, Mann Whitney test or chi-square (χ^2) test to examine the statistical significance of normally distributed data, nonparametric data, or categorical data, respectively. A univariable and multivariable Cox regression analyses were used to examine the predictors of renal stone recurrence. All tests were two-sided and P value of less than 0.05 was considered statistically significant.

All tests used the SPSS version 23 software (IBM SPSS Statistics, IBM Corp., Armonk, NY, USA).

RESULTS

A total of 1260 participants (820 males and 440 females) with history of successful renal stone primary treatment completed the questionnaire and were included in our study. Baseline patients' clinical and demographic data are summarized in (Table I). Median patients' age was 29 years (IQR: 23-41), and median BMI was 25.3 kg/m² (IQR: 21.8-29). The incidence of HTN was 10.2% and PHPT was 5.8%. Most of patients 811 (64.4%) are living in the central region of the country.

Previous primary treatments were PCNL, RIRS, ESWL, surgery and medical treatment in 283 patients (22.5%), 437 patients (34.7%), 334 patients (26.5%), 130 patients (10.3%), and 76 patients (6%), respectively. Among the participants, 383 patients (30.4%) had recurrent renal stone and 877 patients (69.6%) didn't develop recurrence after primary stone treatment. The median follow-up period from the onset of primary stone treatment was 32

Table 1.
Baseline characteristic of patients with renal stone in Saudi Arabia (n = 1260).

Age (yr): mean ± SD median (IQR)	32.5 ± 12.4 29 (23-41)
BMI (kg/m ²): mean ± SD median (IQR)	25.9 ± 6.1 25.3 (21.8-29)
BMI classification, n (%)	
Underweight (< 18.5)	82 (6.5%)
Normal (18.5-24.9)	525 (41.7%)
Overweight and obese (> 25)	653 (51.8%)
Gender, n (%)	
Female	440 (34.9%)
Male	820 (65.1%)
Chronic diseases, n (%)	
HTN	129 (10.2%)
DM	98 (7.8%)
Asthma	106 (8.1%)
Hypercholesterolemia	101 (8%)
PHPT	73 (5.8%)
Gout	27 (2.1%)
Residency, n (%)	
Central region	811 (64.4%)
Eastern region	225 (17.9%)
Western region	125 (9.9%)
Southern region	55 (4.4%)
Northern region	44 (3.5%)
Nationality, n (%)	
Saudi	1191 (94.5%)
Other	69 (5.5%)
Physical activity, n (%)	
Low (≤ 1 day/week)	504 (40%)
Moderate (2-4 days/week)	548 (43.5%)
High (≥ 5 days/week)	208 (16.5%)
Recurrence of kidney stones, n (%)	
First time	877 (69.6%)
Recurrent ≥ 2 times	383 (30.4%)
Family history of renal stone, n (%)	
No	854 (67.8%)
Yes	406 (32.2%)
History of UTI, n (%)	
No	721 (57.2%)
Yes	539 (42.8%)
Dietary habits, n (%)	
High salt diet (> 2 gm/day)	256 (20.3%)
Low fluid intake (< 1 L/day)	459 (36.4%)
High protein intake (≥ 3 times/week)	763 (60.6%)
Low calcium intake (≤ 400 mg/day)	205 (16.3%)
High oxalate containing foods	158 (12.5%)
Stone chemical analysis, n (%)	
Yes	290 (23%)
No	251 (19.9%)
Nobody asked	719 (57.1%)
Stone type, n (%)	
Calcium oxalate	120 (9.5%)
Calcium phosphate	44 (3.5%)
Cystine	54 (4.3%)
Struvite	72 (5.7%)
Unknown	970 (77%)
Metabolic workup, n (%)	
Yes	249 (19.8%)
No	294 (23.3%)
Nobody asked	717 (56.9%)
Previous treatment, n (%)	
PCNL	283 (22.5%)
RIRS	437 (34.7%)
ESWL	334 (26.5%)
Surgery	130 (10.3%)
Controlled diet + medical ttt	76 (6%)

UUS: ultrasound scan, CTU: computed tomography; HTN: hypertension; DM: diabetes mellitus; BMI: body mass index; PHPT: primary hyperparathyroidism; UTI: urinary tract infection; PCNL: percutaneous nephrostomy; RIRS: retrograde intrarenal surgery; ESWL: extracorporeal shockwave lithotripsy.

months (IQR: 24-41). The median time to first recurrence of renal stone was 29 months (IQR: 14-35). After successful primary treatment, 970 (77%) and 1011 (80.2%) of patients didn't have either stone chemical analysis or metabolic work-up, respectively.

The comparison of patients with primary and recurrent renal stones is showed in (Table 2). No significant differ-

Table 2.
Comparing characteristic of patients with first time and recurrent renal stones.

Variables	Primary stone (Group I, n = 877)	Recurrent stone (Group II, n = 383)	P-value
Age (yr), mean ± SD	31.3 ± 12.1	35.1 ± 12.6	0.000
BMI (kg/m ²), mean ± SD	25.9 ± 6.1	26.2 ± 6.3	0.421
BMI classification, n (%)			
Underweight	56 (6.4%)	26 (6.8%)	0.492
Normal	375 (42.8%)	150 (39.2%)	
Overweight and obese	446 (50.9%)	207 (54%)	
Gender, n (%)			0.000
Female	340 (38.8%)	100 (26.1%)	
Male	607 (61.2%)	283 (73.9%)	
Hypertension (HTN), n (%)	73 (8.3%)	56 (14.6%)	0.001
Diabetes (DM), n (%)	63 (7.2%)	35 (9.1%)	0.253
Asthma, n (%)	71 (8.1%)	35 (9.1%)	0.581
Hypercholesterolemia, n (%)	62 (7.1%)	39 (10.2%)	0.071
Hyperparathyroidism, n (%)	41 (4.7%)	32 (8.4%)	0.013
Gout, n (%)	15 (1.7%)	12 (3.1%)	0.137
Residency, n (%)			0.133
Central region	580 (66.1%)	231 (60.3%)	
Eastern region	156 (17.8%)	69 (18%)	
Western region	82 (9.4%)	43 (11.2%)	
Southern region	33 (3.8%)	22 (5.7%)	
Northern region	26 (3%)	18 (4.7%)	
Nationality, n (%)			0.105
Saudi	835 (95.2%)	356 (93%)	
Other	42 (4.8%)	27 (7%)	
Physical activity, n (%)			0.300
Low	363 (41.4%)	141 (36.8%)	
Moderate	371 (42.3%)	177 (46.2%)	
High	143 (16.3%)	65 (17%)	
History of UTI, n (%)			0.005
No	479 (54.6%)	242 (63.2%)	
Yes	398 (45.4%)	141 (36.8%)	
Family history, n (%)			0.101
No	607 (69.2%)	247 (64.5%)	
Yes	270 (30.8%)	136 (35.5%)	
Dietary habits, n (%)			0.782
High salt diet (yes)	180 (20.5%)	76 (19.8%)	
Low fluid intake (yes)	191 (21.8%)	268 (70%)	0.000
High protein intake (yes)	507 (57.8%)	256 (66.8%)	0.003
Low calcium intake (yes)	151 (17.2%)	54 (14.1%)	0.168
High oxalate intake (yes)	105 (12%)	53 (13.8%)	0.358
Stone type, n (%)			0.000
Calcium oxalate	49 (5.6%)	71 (18.5%)	
Calcium phosphate	20 (2.3%)	24 (6.3%)	
Cystine	24 (2.7%)	30 (7.8%)	
Struvite	36 (4.1%)	36 (9.4%)	
Unknown	748 (85.3%)	222 (58%)	
Previous treatment, n (%)			0.654
PCNL	203 (23.1%)	80 (20.9%)	
RIRS	307 (35%)	130 (33.9%)	
ESWL	232 (26.5%)	102 (26.6%)	
Surgery	84 (9.6%)	46 (12%)	
Controlled diet + medical ttt	51 (5.8%)	25 (6.5%)	

UUS: ultrasound scan, CTU: computed tomography; HTN: hypertension; DM: diabetes mellitus; BMI: body mass index; PHPT: primary hyperparathyroidism; UTI: urinary tract infection; PCNL: percutaneous nephrostomy; RIRS: retrograde intrarenal surgery; ESWL: extracorporeal shockwave lithotripsy.

ence was found in most variables ($p > 0.05$). Mean patients' age was 35.1 ± 12.6 yr. in group I compared to 31.3 ± 12.1 yr. in group II ($p = 0.000$). More male patients were present in group II compared to group I (73.9% vs. 61.2%, $p = 0.000$, respectively). The rates of HTN, PHPT, low fluid intake, and high daily protein diet were significantly higher in group II (14.6% vs. 8.3% in group I, $p = 0.001$), (8.4% vs. 4.7% in group I, $p = 0.013$), (70% vs. 21.8% in group I, $p = 0.000$) and (66.8% vs. 57.8% in group I, $p = 0.003$), respectively. Univariate logistic regression analysis showed that age, male patients, HTN, PHPT, history of UTI, low fluid intake, and high daily protein intake were associated with increased risk of renal stones recurrence ($p < 0.05$). Multivariate logistic regression analysis revealed that male patients (OR: 1.686; 95% CI, 1.216-2.337), HTN (OR: 2.342; 95% CI, 1.439-3.812), PHPT (OR: 2.806; 95% CI,

1.510-5.215), low fluid intake (OR: 28.398; 95% CI, 18.158-44.403) and high daily protein intake (OR: 10.058; 95% CI, 6.400-15.807) were predictors of renal stone recurrence.

DISCUSSION

In this prospective study, the risk factors and baseline characteristics of renal stone formers, as well as the predictors of recurrent renal stone formations were investigated in Saudi Arabian. A total of 1260 patients (820 males and 440 females) were included in the analysis. The rate of kidney stone recurrence after successful primary stone treatment was 30.4% among the participants. The results demonstrated that male gender, HTN, PHPT, low oral fluid intake and high daily protein intake were potential risk factors for recurrent kidney stone formation. We believe that the result of our study may provide better insight into the prevention of kidney stones recurrence through proper control and management of its risk factors.

Renal stone recurrence is a common disease. Patients with renal stones have an increase chance of forming another stone in the future. Stones can recur as long as 10 years after the first episode (8). In our cohort, the overall renal stone recurrence rate was 30.4%. Among them, 11.3% of patients had two-time recurrences, 9.8% had three-time recurrences, and 9.4% had four-time recurrences. Our results are in accordance with previous study reporting the recurrence rate of nephrolithiasis recurrence of 38.6% to 53.2% in Saudi Arabia (4). In the present study, the median time of renal stone recurrence was 29 months (IQR: 14-35). Generally, following the initial episode, nephrolithiasis carries a high recurrence rate of 3.4 per 100 person-years, 7.1 after the second episode, 12.1 after the third episode, and 17.6 after the fourth episode or higher (15). Moreover, the natural cumulative recurrence stone rate was estimated to be 6 to 17%, 35%, and 52% at one year, five years, and ten years, respectively (15).

Our study showed that the recurrent kidney stone rate was found to be significantly higher in men (56.6%) than in women (44.4%). In addition, male gender was identified as a predictor for nephrolithiasis recurrence. This may be attributed to the hormonal differences between men and women. In women, estrogen stimulates the secretion of citric acid in urine and regulates the synthesis of 1,25-dihydroxy-vitamin D which are considered protective factors against nephrolithiasis. On the other hand, men's androgen induces the urinary accumulation of uric acid, calcium, and oxalate which increase the risk of kidney stone formation (16, 17).

Of note, 10.2% of the cases in our study had HTN and the odds of recurrent renal stone in HTN cases was 2.34 compared with non-HTN cases. *Sahng et al.* found that the risk of renal stone formation was directly associated with the incidence of HTN (18). Interestingly, in a recent study 29.7% of patients with nephrolithiasis had HTN (19). In a recent systematic review and meta-analysis, HTN was found to be one of the risk factors for renal stone recurrence (20). It worth note that, the exact mechanism of renal stone formation in patients with HTN remains unclear, and only few studies have examined it.

Table 3.

Univariate and multivariate analysis of predictors of recurrent renal stone ≥ 2 times in Saudi patients.

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.025 (1.015-1.035)	0.000		
BMI	1.008 (0.989-1.028)	0.421		
BMI classification:				
Underweight	Ref			
Normal	0.862 (0.521-1.424)	0.561		
Overweight and obese	1.000 (0.610-1.637)	0.999		
Male patient	1.794 (1.401-2.298)	0.000	1.686 (1.216-2.337)	0.002
HTN	1.886 (1.301-2.734)	0.001	2.342 (1.439-3.812)	0.001
DM	1.299 (0.844-2.001)	0.234		
Asthma	0.142 (0.747-1744)	0.540		
Hypercholesterolemia	1.490 (0.979-2.268)	0.063		
PHPT	1.859 (1.152-3.001)	0.011	2.806 (1.510-5.215)	0.001
Gout	1.859 (0.862-4.010)	0.114		
Residency:				
Central region	Ref			
Eastern region	1.111 (0.805-1.532)	0.523		
Western region	1.738 (0.935-3.231)	0.081		
Southern region	1.647 (0.956-2.932)	0.072		
Northern region	1.317 (0.883-1.963)	0.177		
Saudi patient	0.663 (0.403-1.092)	0.107		
Physical activity:				
Low	Ref			
Moderate	1.228 (0.943-1.600)	0.127		
High	1.170 (0.823-1.664)	0.381		
History of UTI	1.426 (1.114-1.825)	0.005		
Renal stone Family history	1.238 (0.960-1.595)	0.099		
Dietary habits:				
High salt diet	0.959 (0.710-1.294)	0.782		
Low fluid intake	8.370 (6.383-10.976)	0.000	28.398 (18.158-44.403)	0.000
High protein intake	1.471 (1.144-1.892)	0.003	10.058 (6.400-15.807)	0.000
Low calcium intake	0.789 (0.563-1.105)	0.168		
High oxalate intake	1.181 (0.828-1.683)	0.358		
Previous treatment:				
PCNL	Ref			
RIRS	1.075 (0.772-1.495)	0.670		
ESWL	1.116 (0.788-1.580)	0.538		
Surgery	1.390 (0.892-2.164)	0.145		
Diet + medical ttt	1.244 (0.722-2.143)	0.432		

UUS: ultrasound scan; CTU: computed tomography; HTN: hypertension; DM: diabetes mellitus; BMI: body mass index; PHPT: primary hyperparathyroidism; UTI: urinary tract infection; PCNL: percutaneous nephrostomy; RIRS: retrograde intrarenal surgery; ESWL: extracorporeal shockwave lithotripsy.

Frequent changes in the levels of blood pressure have a direct effect on the urinary microbiomes, which may stimulate nephrolithiasis (21).

Dietary habits play an important role in the renal stone formation. Excessive meat consumption and low fluid intake were considered as main risk factors for nephrolithiasis. Our study showed that in patients with recurrent kidney stones high protein intake rate was significantly higher (66.8%) than in primary stone formers (57.8%), similarly low fluid intake was significantly higher (70% vs. 21.8%). High protein intake leads to acidification of urine, which stimulate the formation of calcium oxalate stone (22). Xu *et al.* found that each 500 mL increase in water intake was significantly associated with a reduced risk of kidney stone formation (RR = 0.93; 95% CI: 0.87, 0.98; $p < 0.01$). Additionally, daily water intake > 2000 mL decreases the risk of first kidney stone formation by at least 8% compared to 1500 mL (23).

PHPT is one of the listed risk factors for renal stone formation. It has been estimated that 20% of patients with PHPT have nephrolithiasis, and approximately 5% of patients who presented with renal stones have PHPT (24). Our results are in agreement with the aforementioned results. Notably, 73 patients (5.8%) have PHPT in our cohort analysis. Moreover, the rate of patients with recurrent renal stone and PHPT was significantly higher (8.4%) than those without PHPT (4.7%), in addition, the odds of recurrent renal stone in PHPT patients was 2.8 compared with non-PHPT patients.

The current study has limitations and strengths. The strength points of our study are the following: a prospective study, large sample size ($n = 1260$), and extensive data gathering for the factors of interest related to stone formation and recurrence (e.g., age, sex, BMI, medical comorbidities, dietary habits, area of residency etc.). However, our study does not devoid of limitations, and the results have to be interpreted with caution. For instance, the short median follow-up period (32 months) may be not enough to estimate the actual rate of renal stone recurrence. Non-recurrent stone formers in this study are “patients who formed a first stone” although they may develop stone recurrence after longer follow-up period. Also, stone composition and metabolic work-up results are unknown in 77% and 80.2% of patients, respectively. Excluding those patients was not possible to complete the analysis.

On the other hand, these findings raise an important concern regarding urologists practice in Saudi Arabia where best clinical practice guidelines regarding metabolic work-up and stone chemical analysis are underutilized and need to be applied by our urologists extensively among stone former patients.

CONCLUSIONS

Our study revealed that male gender, hypertension, primary hyperparathyroidism, low fluid intake and high daily protein intake are factors potentially increasing the risk of renal stone recurrence among Saudi Arabian patients. Being aware of these risk factors can provide proper guidance for the prevention of nephrolithiasis recurrence and its management.

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