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Original Article

Research on the relationship between urinary citrate/urinary calcium ratio and postoperative recurrence of ureteral calculus

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Abstract: Objective: Our aim was to investigate the effect of 24-hour urinary citrate/urinary calcium ratio on recurrence of ureteral calculus. Methods: A total of 100 patients with ureteral calculus, determined to be free from residual calculus after being applied Extracorporeal Shock Wave Lithotripsy in Changzhou Wujin Hospital Affiliated to Jiangsu University, were selected as research objects. They were randomly divided into a control group and research group, with 50 patients in each group. In addition, 50 local healthy volunteers were enrolled. The observation group took potassium citrate 2 g/time for 3 times/day for continuous administration, as directed by the doctor after routine operation of ureteral calculus. Patients in the control group and observation group were tested for urinary pH values, urinary calcium, urinary acid, and citrate and urinary citrate/urinary calcium in the 24 hours prior to treatment. These were re-determined at the 6th month, 12th month, and 24th month after treatment. We conducted a statistical analysis for recurrence rate of patients in the corresponding time period. Results: The observation group was significantly higher than the control group in pH, 24 h sodium citrate, and 24 h urinary citrate/urinary calcium ratio but lower than the control group in 24 h urinary calcium (all $P<0.05$). The healthy group was similar to treated observation group in pH, 24 h urinary citrate, 24 h urinary calcium, and 24 h urinary citrate/urinary calcium ratio (all $P>0.05$) but significantly different from control group (all $P<0.05$). The control group had a recurrence rate of 34.00% with 17 cases involved, while the observation group had a recurrence rate of 6.00% with 3 cases involved. Recurrence time of calculus was positively correlated to urinary pH, 24 h urinary citrate, and 24 h urinary citrate/urinary calcium ratio. It was negatively correlated to 24 h urinary calcium and irrelevant to uric acid level. Conclusion: 24 h urinary citrate, urinary calcium, and 24 h citrate/urinary calcium ratio are closely related to recurrence of ureteral calculus. They can be used as a monitoring index, clinically, and are of great significance in timely detecting recurrence of ureteral calculus.

Keywords: 24 h citrate/urinary calcium, ureteral calculus, prognosis, recurrence

Introduction

Urinary calculus is a common disease of the urinary system. Epidemiological studies have shown that the number of patients with calculus has increased in recent years with an incidence rate of about 10% in some high-prevalence areas. This disease easily relapses after the cure, seriously affecting patient physical health, mental health, and economic status [1, 2]. Extracorporeal Shock Wave Lithotripsy (ESWL) is the first choice of treatment for infection of the upper urinary tract. It has the advantage of a high rate of expelling calculus. It is a simple operation with little trauma but has not solved the problem of high recurrence rate [3, 4]. Therefore, how to detect early and effectively prevent calculus recurrence has become a key clinical problem yet to be solved. Many research results have presented that low citrate and high calcium are influencing factors of urolithiasis, in which citrate can inhibit urolithiasis while urinary calcium can promote urolithiasis [5-7]. This paper aimed to find the relationship between citrate and urinary calcium levels and prognosis and recurrence of ureteral calculus.

Table 1. General data comparison ($\bar{x}$ ± sd; n, %)

Group	Control group	Observation group	χ^2	P
Case	50	50		
Calculus diameter (cm)	1.27 ± 0.15	1.29 ± 0.11	0.5081	0.3069
Calculus type				
Calcium-bearing stones	35 (70.00)	31 (62.00)	0.7130	0.3984
Calculus urate	12 (24.00)	14 (28.00)	0.2079	0.6484
Other	3 (6.00)	5 (10.00)	0.5435	0.4610

Table 2. Other general data comparison ($\bar{x}$ ± sd)

Index	Case	Control group	Observation group	Healthy group
Age (years)	50	46.97 ± 8.68	51.88 ± 11.78	49.62 ± 11.26
Gender (female/male)	50	18/32	20/30	24/26
Weight (kg)	50	75.80 ± 12.21	79.66 ± 12.40	78.43 ± 8.99
BMI (kg/m^2)		21.48 ± 4.57	20.73 ± 1.47	24.15 ± 2.70

Note: BMI, body mass index.

Materials and methods

General data

This research was approved by the Ethics Committee of Changzhou Wujin Hospital, Affiliated to Jiangsu University. A total of 100 patients with ureteral calculus treated in Changzhou Wujin Hospital, Affiliated to Jiangsu University, from January 2013 to January 2015, were selected as research objects. Patients were randomly divided into the control group and observation group, with 50 patients in each group.

Inclusion criteria: (1) Anyone diagnosed with only ureteral calculus by preoperative B ultrasound, plain abdominal radiograph, and radiography; (2) Patients who were operated with ESWL in Changzhou Wujin Hospital, Affiliated to Jiangsu University, and verified that there were no complications such as residual calculus and infection effect after operation; (3) Anyone willingly participating in this research signed an informed consent form.

Exclusion criteria: (1) Patients with serious basic systemic diseases such as heart, liver, and kidney diseases; (2) Anyone with electrolyte disruption or taking medicines with an effect on electrolytes; (3) Anyone with potassium citrate allergy; (4) Pregnant or lactating women.

Research methods

After the two groups of patients were confirmed to be free from residual calculus, potassium citrate was administrated to the observation group 2 g/time and 3 times/day after meals. Dosage was adjusted before being taken, according to urinary pH, to maintain the pH between 6.5-7.0. Daily water intake was not less than 2,000 mL, with keeping medication, during the treatment for a 7.6 months average. Placebo was administrated to the control group with same usage and dosage as those of the observation group. The healthy group was composed of enrolled health examination volunteers.

Observation indexes

24 h urinary pH, urinary calcium, uric acid, and citrate were determined for research objects in observation group, control group, and healthy group prior to treatment. 24 h urinary pH, urinary calcium, uric acid, and citrate were collected in the 3rd month, 6th month, 12th month, and 24th month with statistics conducted for recurrence rate in the corresponding period. Statistical analysis on all biochemical indexes of recurrent patients at last examination and patients without recurrence at the 24th month was performed to analyze correlation between recurrence and the tested biochemical indexes.

Statistical methods

SPSS21.0 software was used for statistical analysis. Measurement data was expressed as mean ± standard deviation ($\bar{x}$ ± sd) and t-test was applied. Enumeration data was expressed as a percentage and X^2 test was applied. $P<0.05$ represented a difference of statistical significance. Bio-chemical indexes (24 h urinary pH, urinary calcium, uric acid, citrate, and citrate/urinary calcium ratio) of recurrent patients at last examination and patients without recurrence at 24th month were selected to be analyzed with Spearman's rank test in SPSS, in order to analyze correlation between bio-chemical indexes and patient recur-

Table 3. Comparison of changes in biochemical indexes ($\bar{x}$ ± sd)

Group	pH	Uric acid (μmol/L)	24 h urine citrate (mg)	24 h urinary calcium (mmol)	24 h urinary citrate/ urinary calcium ratio
Control group					
Before treatment	5.13 ± 0.33^{b}	323.46 ± 38.69	263.72 ± 27.28^{b}	7.59 ± 0.96^{b}	35.45 ± 5.53^{b}
6 months	5.36 ± 0.28^{b}	328.24 ± 40.63	278.92 ± 45.51^{b}	7.19 ± 1.07^{b}	39.85 ± 9.27^{b}
12 months	5.43 ± 0.34^{b}	318.02 ± 44.68	274.42 ± 41.79^{b}	7.81 ± 1.06^{b}	35.94 ± 7.46^{b}
24 months	5.30 ± 0.26^{b}	326.82 ± 49.14	273.24 ± 38.22^{b}	7.29 ± 0.87^{b}	37.93 ± 6.55^{b}
Observation group					
Before treatment	5.19 ± 0.64^{b}	323.41 ± 30.47	246.38 ± 56.86^{b}	6.96 ± 0.96^{b}	36.84 ± 12.09^{b}
6 months	6.49 ± 0.49^{a,c}	319.81 ± 36.55	362.69 ± 49.96^{a,c}	5.82 ± 0.76^{a,c}	63.54 ± 12.81^{a,c}
12 months	6.76 ± 0.63^{a,c}	318.52 ± 32.14	363.42 ± 47.556^{a,c}	5.38 ± 0.68^{a,c}	68.91 ± 14.38^{a,c}
24 months	6.44 ± 0.69^{a,c}	317.04 ± 33.71	353.76 ± 34.65^{a,c}	5.88 ± 0.90^{a,c}	61.19 ± 10.28^{a,c}
Healthy group	6.69 ± 0.59^{a,c,d}	324.17 ± 38.40	334.89 ± 28.98^{a,c,d}	5.63 ± 0.54^{a,c,d}	60.18 ± 8.08^{a,c,d}

Note: Compared with the control group in the same period after intervention, ^{a}P<0.05; compared with the healthy group, ^{b}P<0.05; compared with the observation group before intervention, ^{c}P<0.05; compared with the control group, ^{d}P<0.05.

Table 4. Recurrence comparison of two groups of patients (n, %)

Group	Case	3 months	6 months	12 months	24 months	Total recurrence rate (%)
Control group	50	0	3 (6.00)	6 (12.00)	8 (16.00)	34.00
Observation group	50	0	0	1 (2.00)	2 (4.00)	6.00
χ^2			3.0928	3.8402	4.0000	11.9304
P			0.0786	0.0500	0.0455	0.0006

Table 5. Analysis of correlation between biochemical indexes and recurrence time

Index	Uric acid	Uric pH	24 h urine citrate	24 h urinary calcium	24 h urinary citrate/ urinary calcium ratio
R	-0.2530	0.6740	0.7412	-0.8413	0.6328
P	0.0612	0.0011	0.0002	<0.0001	0.0027

rence time. P<0.05 was considered statistically significant.

Results

General data comparison

Prior to operation, there was no statistical difference between the two groups of patients in calculus diameter and type (all P>0.05). They had normal renal function without symptoms of hydronephrosis. There was no difference in age, gender, body weight, and body mass index among the three groups (all P>0.05). There was no statistical significance and subsequent experimental data was comparable. See **Tables 1** and **2**.

Change in biochemical index

Prior to treatment, the control group was similar to observation group in urinary pH, uric acid, 24 h urine citrate, 24 h urinary calcium, and 24 h urinary citrate/urinary calcium ratio (all P>0.05). After treatment, the observation group was significantly higher than control group in pH, 24 h sodium citrate, and 24 h urinary citrate/urinary calcium ratio but lower than the control group in 24 h urinary calcium. The healthy group was similar to observation group in urinary pH, 24 h urinary citrate, 24 h urinary calcium, and 24 h urinary citrate/urinary calcium ratio but significantly different from the control group after intervention. See **Table 3**.

Recurrence comparison

No recurrence occurred in both groups within 3 months after operation, with 3 recurrence cases in the control group in the 6th month after operation (P>0.05) and 1 recurrence case in observation group in the 12th month after operation (P=0.05). Recurrence rate of the observa-

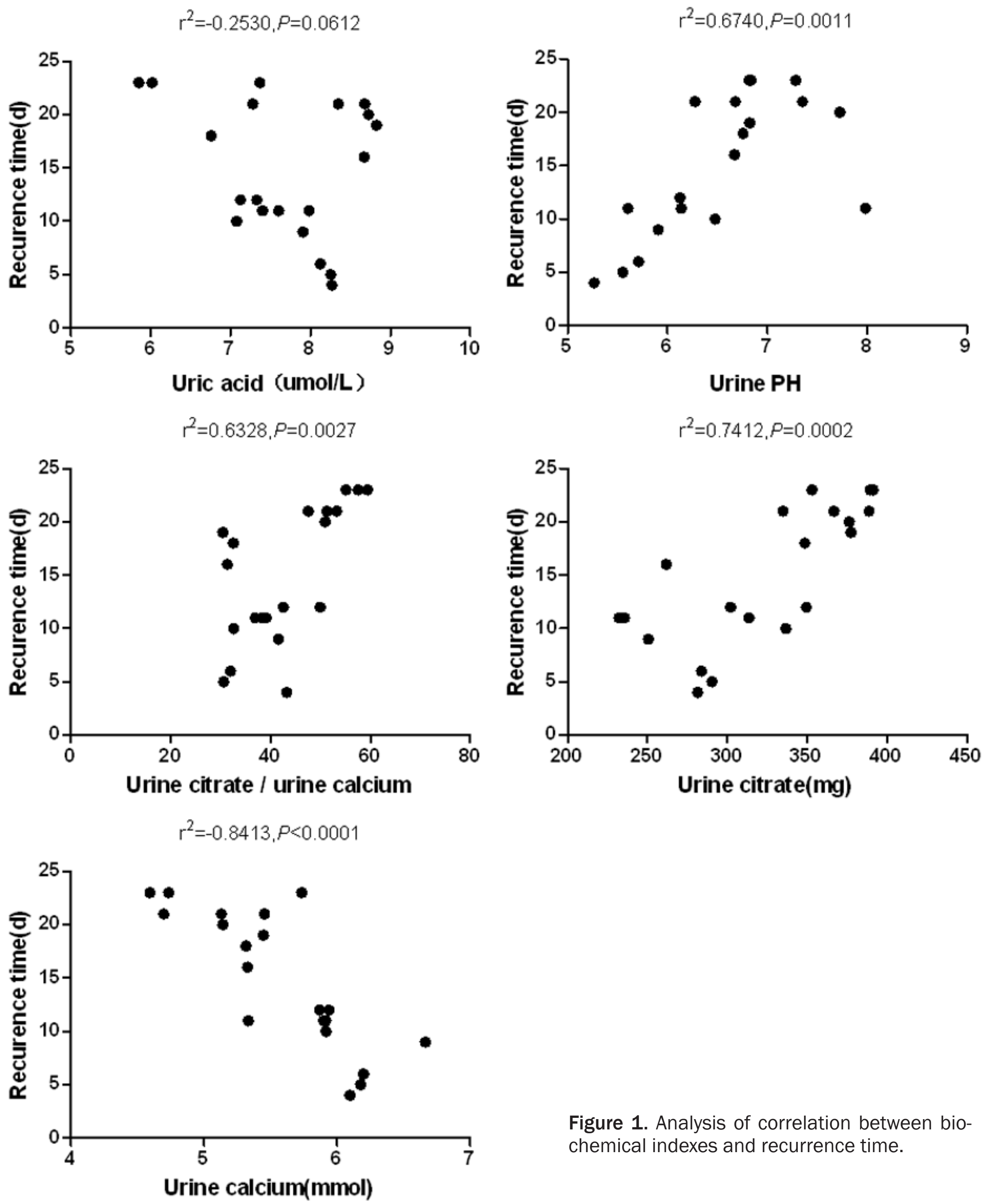

Figure 1. Analysis of correlation between biochemical indexes and recurrence time.

tion group was significantly lower than the control group within 2 years, which had a statistical difference (P<0.05). See **Table 4**.

Analysis of the correlation between biochemical indexes and recurrence time

Recurrence time of calculus was positively correlated to urinary pH, 24 h urinary citrate, and 24 h urinary citrate/urinary calcium ratio but negatively correlated to 24 h urinary calcium. It was irrelevant to uric acid level. The higher the 24 h urinary citrate and 24 h urinary citrate/urinary calcium ratio, the later recurrence time of calculus would be. See **Table 5** and **Figure 1**.

Discussion

With enrichment of experience in clinical drug treatments and continuous optimization of lithotripsy and laparoscopy, ESWL, percutaneous nephrolithotomy, and ureteroscopic lithotripsy or lithotripsy have gradually become widely used in clinical practice [8-12]. Previous open operations for calculus removal have been phased out. Although we have made some breakthroughs in therapies of urolithiasis, we must clearly recognize that these therapies have not effectively prevented occurrence and recurrence of urolithiasis and some even have increased probability of recurrence. A report written by Kamihira et al. showed that the recurrence rate of calculus exceeded 6% in the first year and was up to 41.8% in the 5th year after ESWL [13]. In addition, Abe et al. performed long-term follow up for patients with calculus of upper urinary tract, that had been operated with ESWL, and results showed that recurrence rate of calculus exceeded 7% in the first year, 24.1% in the 3rd year, and 33% in the 5th year after operation [14]. Therefore, finding effective detection indexes to further assist in diagnosis of recurrent urinary calculus has become a large problem yet to be solved.

Causes of urolithiasis are complex but the vast majority of urolithiasis comes from mineralization of the body's own metabolites and is closely related to metabolic disorders, environmental conditions, and eating habits. When urolithiasis promoters in urine are excessive or inhibitors are insufficient, the signaling pathway which promotes calculus growth will be induced to open [15]. Potassium citrate has gradually gained more and more clinical attention due to its advantages of low cost, less adverse reactions, and good clinical effect. Its mechanism of efficacy is mainly as follows: part of potassium citrate can be absorbed in the body and decomposed into citrate radical and potassium ions through oxygenolysis, in which citrate radical can be combined with H^+ to increase pH of the urine to relieve symptoms of acidosis, while potassium ions are rapidly metabolized in the blood so that serum potassium concentration is not affected [16]. High concentrations of potassium in urine can promote the renal tubular to reabsorb calcium, thereby reducing urinary calcium concentration. Part of potassium citrate, not decomposed in body through oxygenolysis, is directly discharged from the urine, which increases the concentration of urinary citrate, inhibiting urolithiasis [17]. In addition, some researchers have found that potassium citrate can change the TH protein so that it can play a role in inhibiting urolithiasis [18]. Pak et al. administrated potassium citrate (about 6.0 g/d) to patients with merged low citrate urine calcium calculus for treatment and found that treated patients have normal serum potassium, sodium and other electrolytes, increased urinary pH value, and normal citrate. He also found that potassium citrate effectively inhibits calculus growth and recurrence [19, 20]. Scales et al. also confirmed that citrate levels in patients who have taken potassium citrate increase to normal range and urolithiasis rate is significantly reduced with good effects [21, 22]. However, the above studies involve fewer detection indexes and lack comparisons with healthy population data. Therefore, we compared urinary citrate and urinary calcium values in patients that have and have not been administrated citrate with healthy examination population. In this manner, the clinical index for prognosis, effect, and recurrence of ureteral calculus can be better reflected.

Our research results show that patients of the control group had a higher level of urinary calcium and lower citrate level and urinary pH while patients in observation group, who were administered potassium citrate, had higher level of citrate and significantly lower level of urinary calcium than those of the control group. It had statistical difference (both $P<0.05$) and was consistent with findings of domestic scholars, indicating that patients with calculus who were treated with operation were in imbalance between urolithiasis promoters and inhibitors and the concentration of urolithiasis substance was excessive and in supersaturation [23]. This also suggests that risk of calculus recurrence should be considered clinically when citrate and urinary calcium and other indexes changes significantly. It was also found in this research that indexes, other than uric acid level (which did not change), such as citrate, urinary calcium, and 24 h citrate/urinary calcium ratio were related to calculus recurrence. Citrate, urinary pH, and 24 h citrate/urinary calcium ratio of recurrent patients with calculus decreased and was positively correlated to recurrence time, while their urinary calcium levels increased and was negatively correlated to recurrence. 24 h citrate/urinary calcium ratio was most related to recurrence. This index can better reflect whether urolithiasis promoters in urine were in supersaturation and whether it was unbalanced with its opposite force, namely crystallization inhibiter, which can effectively predict risk of calculus recurrence.

This study, however, was limited by the small number in the study population, short follow up time, unguaranteed patient compliance, and other relevant factors. Therefore, further controlled research should be carried out to determine whether 24 h citrate/urinary calcium ratio can be used as an effective index to prevent calculus recurrence and be popularized and applied clinically. In the future, we will carry out an epidemiological investigation for local patients with urinary calculus to determine factors affecting urolithiasis and perform unconditional logistic regression analysis with single factor and multiple factors to determine the relative importance of risk factors in incidence of urolithiasis. Key prevention measures will be worked out to reduce incidence of urolithiasis. Moreover, previous studies will be combined with our research to create a new pattern to prevent and control urinary calculus, avoiding its recurrence in this region.

In conclusion, 24 h urinary citrate, urinary calcium, and 24 h citrate/urinary calcium ratio are closely related to recurrence of ureteral calculus. They can be used as monitoring indexes, clinically, and are of great significance in timely detecting recurrence of ureteral calculus.

Disclosure of conflict of interest

None.

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References

[1] Ziemba JB and Matlaga BR. Guideline of guidelines: kidney stones. BJU Int 2015; 116: 184-189.
[2] Turk C, Petrik A, Sarica K, Seitz C, Skolarikos A, Straub M and Knoll T. EAU guidelines on interventional treatment for urolithiasis. Eur Urol 2016; 69: 475-482.
[3] Cecen K, Karadag MA, Demir A, Bagcioglu M and Kocaaslan R. Erratum to: flexible ureterorenoscopy versus extracorporeal shock wave lithotripsy for the treatment of upper/middle calyx kidney stones of 10-20 mm: a retrospective analysis of 174 patients. Springerplus 2016; 5: 484.
[4] Ster A, Safranko S, Bilic K, Markovic B and Kralj D. The effect of hydrodynamic and thermodynamic factors and the addition of citric acid on the precipitation of calcium oxalate dihydrate. Urolithiasis 2017; [Epub ahead of print].
[5] Siener R. Can the manipulation of urinary pH by beverages assist with the prevention of stone recurrence? Urolithiasis 2016; 44: 51-56.
[6] Gambaro G, Croppi E, Coe F, Lingeman J, Moe O, Worcester E, Buchholz N, Bushinsky D, Curhan GC, Ferraro PM, Fuster D, Goldfarb DS, Heilberg IP, Hess B, Lieske J, Marangella M, Milliner D, Preminger GM, Reis Santos JM, Sakhaee K, Sarica K, Siener R, Strazzullo P and Williams JC. Metabolic diagnosis and medical prevention of calcium nephrolithiasis and its systemic manifestations: a consensus statement. J Nephrol 2016; 29: 715-734.
[7] Skolarikos A, Straub M, Knoll T, Sarica K, Seitz C, Petrik A and Turk C. Metabolic evaluation and recurrence prevention for urinary stone patients: EAU guidelines. Eur Urol 2015; 67: 750-763.
[8] Srisubat A, Potisat S, Lojanapiwat B, Setthawong V and Laopaiboon M. Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones. Cochrane Database Syst Rev 2014; Cd007044.
[9] Armagan A, Tepeler A, Silay MS, Ersoz C, Akcay M, Akman T, Erdem MR and Onol SY. Micropercutaneous nephrolithotomy in the treatment of moderate-size renal calculi. J Endourol 2013; 27: 177-181.
[10] Fuller A, Razvi H, Denstedt JD, Nott L, Hendrikx A, Luke M, Pal SK and de la Rosette J. The clinical research office of the endourological society percutaneous nephrolithotomy global study: Outcomes in the morbidly obese patient - a case control analysis. Can Urol Assoc J 2014; 8: E393-397.
[11] Tepeler A, Akman T, Silay MS, Akcay M, Ersoz C, Kalkan S, Armagan A and Sarica K. Comparison of intrarenal pelvic pressure during micro-percutaneous nephrolithotomy and conventional percutaneous nephrolithotomy. Urolithiasis 2014; 42: 275-279.
[12] Jiang JT, Li WG, Zhu YP, Sun WL, Zhao W, Ruan Y, Zhong C, Wood K, Wei HB, Xia SJ and Sun XW. Comparison of the clinical efficacy and safety of retroperitoneal laparoscopic ureterolithotomy and ureteroscopic holmium laser lith-

otripsy in the treatment of obstructive upper ureteral calculi with concurrent urinary tract infections. Lasers Med Sci 2016; 31: 915-920.
[13] Kamihira O, Ohshima S, Ono Y, Katoh N, Matsuura O, Takeuchi N, Takeda A, Yamada S, Kuriki O and Hashimoto Y. ESWL treatment and the detection of urological neoplasms. Japanese Journal of Endourology & Eswl 1996; 9: 105-108.
[14] Abe T, Go R, Mori K and Kohyama A. Epidural fentanyl provide sufficient analgesia for extracorporeal shock wave lithotripsy (ESWL). Masui 1997; 46: 694-699.
[15] Raja A, Hekmati Z and Joshi HB. How do urinary calculi influence health-related quality of life and patient treatment preference: a systematic review. J Endourol 2016; 30: 727-743.
[16] Havlin J, Matousovic K, Vankova S and Schuck O. Metabolic acidosis in chronic kidney disease. Vnitr Lek 2016; 62: 30-39.
[17] Lojanapiwat B, Tanthanuch M, Pripathanont C, Ratchanon S, Srinualnad S, Taweemonkongsap T, Kanyok S and Lammongkolkul S. Alkaline citrate reduces stone recurrence and regrowth after shockwave lithotripsy and percutaneous nephrolithotomy. Int Braz J Urol 2011; 37: 611-616.
[18] Chariyavilaskul P, Poungpairoj P, Chaisawadi S, Boonla C, Dissayabutra T, Prapunwattana P and Tosukhowong P. In vitro anti-lithogenic activity of lime powder regimen (LPR) and the effect of LPR on urinary risk factors for kidney stone formation in healthy volunteers. Urolithiasis 2015; 43: 125-134.
[19] Pak CY, Odvina CV, Pearle MS, Sakhaee K, Peterson RD, Poindexter JR and Brinkley LJ. Effect of dietary modification on urinary stone risk factors. Kidney Int 2005; 68: 2264-2273.
[20] Brardi S, Imperiali P, Cevenini G, Verdacchi T and Ponchietti R. Effects of the association of potassium citrate and agropyrum repens in renal stone treatment: results of a prospective randomized comparison with potassium citrate. Arch Ital Urol Androl 2012; 84: 61-67.
[21] Scales CD Jr, Smith AC, Hanley JM and Saigal CS. Prevalence of kidney stones in the United States. Eur Urol 2012; 62: 160-165.
[22] Carvalho M, Erbano BO, Kuwaki EY, Pontes HP, Liu J, Boros LH, Asinelli MO and Baena CP. Effect of potassium citrate supplement on stone recurrence before or after lithotripsy: systematic review and meta-analysis. Urolithiasis 2017; 45: 449-455.
[23] Shi HL, Mo NX, Chen BL, Xu RF, Zou JG, Wang XG and Mao WJ. Factors influencing the formation of urinary tract stones and the effects of sodium citrate and potassium sodium intervention. Jiangsu Medicine 2016; 42: 590-592.