Hypocitraturia and hypokaliuria : major metabolic risk factors for kidney stone disease

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Objective : *Kidney stone disease has high rates of recurrence. In order to avert a recurrent episode, metabolic risk factors should be evaluated during follow-up. The study is aimed to investigate the metabolic abnormalities in patients with kidney stone and to explore whether metabolic disorders are associated with types of the stone.*

Methods : *A total of 34 patients with renal stone were recruited in the study and 24-hour urine and stone specimens were collected. Most patients (52 %) resided in the central region of Thailand. Thirty-two healthy controls participated and their 24-hour urine samples were also collected. Metabolic abnormalities including hypercalciuria, hyperoxaluria, hyperphosphaturia, hyperuricosuria, hypocitraturia, hypokaliuria and hypomagnesiuria were assessed. Urine volume and pH were also determined and the type of stone was analyzed using a Fourier transformed infrared spectrometry.*

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Results : *Urine volume of renal stone patients was significantly less than that of healthy controls (P = 0.006). The prevalence of hypercalciuria, hyperoxaluria, hyperphosphaturia, hyperuricosuria and hypomagnesiuria in healthy and stone patients was not statistically different. Hypocitraturia (100 %) and hypokaliuria (79.4 %) were remarkably observed in kidney stone patients. Calcium oxalate, magnesium ammonium phosphate (or struvite) and uric acid stones were accounted for 67 % (23/34), 18 % (6/34) and 15 % (5/34), respectively. Associations between metabolic abnormalities and stone types were not shown. Acidic urinary pH (median: 5.44; min-max: 5.25-5.99) was significantly related to uric acid stone whereas an increased urinary pH (median: 6.86; min-max: 6.55-9.10) was correlated to struvite stone.*

Conclusion : *Metabolic disorders did not determine the type of stone. Acidic urine indicated the preference of uric acid stone formation while alkali urine promoted the development of struvite stone. Hypocitraturia and hypokaliuria were considered the main metabolic risk factors of kidney stone in Thai patients, and low urine excretion was also an important stone risk. Metabolic evaluation and modification in dietary habit as well as potassium citrate supplementation are recommended for effective therapeutic managements of kidney stone.*

Keywords : *Hypocitraturia, Hypokaliuria, Kidney stone, Risk factor, Metabolic abnormality.*

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พันธ์ทิพย์ ยังเจิมจันทร์, สมเกียรติ พุ่มไพศาลชัย, สุพจน์ รัชชานนท์, พงศ์ศักดิ์ พันธุ์สิน, ปิยะรัตน์ โตสุโขวงศ์, เกรียง ตั้งสง่า, ชาญชัย บุญหล้า. ภาวะซิเทรตในปัสสาวะต่ำและภาวะโพแทสเซี่ยมในปัสสาวะต่ำเป็นปัจจัยเสี่ยงทางเมแทบอลิกที่สำคัญของโรคนิ่วไต. จุฬาลงกรณ์เวชสาร 2549 ก.ย; 50(9): 605 – 21

วัตถุประสงค์ : *โรคนิ่วไตมีอัตราการเป็นนิ่วซ้ำสูง เพื่อให้การรักษาที่เหมาะสมและลดโอกาสการเกิดนิ่วซ้ำควรมีการประเมินภาวะความผิดปกติทางเมแทบอลิกในผู้ป่วยโรคนิ่วไตระหว่างการติดตามผล การศึกษานี้มีวัตถุประสงค์เพื่อตรวจสอบความผิดปกติทางเมแทบอลิกของผู้ป่วยโรคนิ่วไตเทียบกับกลุ่มคนปกติ และประเมินว่าความผิดปกติทางเมแทบอลิกมีความสัมพันธ์กับชนิดของก้อนนิ่วหรือไม่*

วิธีการ : *จำนวนผู้ป่วยโรคนิ่วไตที่ทำการศึกษาทั้งหมด 34 ราย เก็บตัวอย่างก้อนนิ่วและปัสสาวะ 24 ชั่วโมง ผู้ป่วยส่วนใหญ่ (52 %) มีภูมิลำเนาในภาคกลาง กลุ่มควบคุมคนปกติมีจำนวน 32 ราย และเก็บตัวอย่างปัสสาวะ 24 ชั่วโมง ตรวจประเมินความผิดปกติทางเมแทบอลิก ได้แก่ ภาวะแคลเซี่ยมในปัสสาวะสูง ภาวะออกซาเลตในปัสสาวะสูง ภาวะฟอสเฟตในปัสสาวะสูง ภาวะกรดยูริกในปัสสาวะสูง ภาวะซิเทรตในปัสสาวะต่ำ ภาวะโพแทสเซี่ยมในปัสสาวะต่ำ และภาวะแมกนีเซี่ยมในปัสสาวะต่ำ ในตัวอย่างปัสสาวะของกลุ่มตัวอย่าง วัดปริมาตรปัสสาวะ 24 ชั่วโมงและความเป็นกรด-ด่าง และวิเคราะห์ชนิดของก้อนนิ่วโดยวิธี Fourier transformed infrared spectrometry*

ผลการทดลอง : *ปริมาตรของปัสสาวะ 24 ชั่วโมงของผู้ป่วยโรคนิ่วไตน้อยกว่าคนปกติอย่างมีนัยสำคัญ (P = 0.006) ความชุกของภาวะแคลเซี่ยมในปัสสาวะสูง ภาวะออกซาเลตในปัสสาวะสูง ภาวะฟอสเฟตในปัสสาวะสูง ภาวะกรดยูริกในปัสสาวะสูง และภาวะแมกนีเซี่ยมในปัสสาวะต่ำไม่แตกต่างกันอย่างมีนัยสำคัญระหว่างในผู้ป่วยโรคนิ่วไตและคนปกติ สำหรับภาวะซิเทรตในปัสสาวะต่ำ (100%) และภาวะโพแทสเซี่ยมในปัสสาวะต่ำ (79.4 %) พบสูงมากในผู้ป่วยโรคนิ่วไต จากการวิเคราะห์ก้อนนิ่วพบนิ่วแคลเซี่ยมออกซาเลต นิ่วแมกนีเซี่ยมแอมโมเนี่ยมฟอสเฟต (หรือนิ่วสตรูไวท์) และนิ่วกรดยูริก ร้อยละ 67 (23/34), 18 (6/34) และ 15 (5/34) ตามลำดับ ไม่พบความสัมพันธ์ระหว่างความผิดปกติทางเมแทบอลิกและชนิดของก้อนนิ่ว ภาวะปัสสาวะเป็นกรด (median pH; 5.44, min-max; 5.25-5.99) สัมพันธ์อย่างมีนัยสำคัญกับนิ่วกรดยูริก ขณะที่ปัสสาวะที่มีค่าความเป็นกรด-ด่างสูงขึ้น (median pH; 6.86, min-max; 6.55-9.10) สัมพันธ์กับนิ่วสตรูไวท์*

สรุปผล : *ความผิดปกติทางเมแทบอลิกไม่สามารถบ่งบอกชนิดของก้อนนิ่วได้ อย่างไรก็ตามปัสสาวะที่เป็นกรดบ่งชี้การชอบเป็นนิ่วชนิดกรดยูริก ขณะที่ปัสสาวะที่เป็นด่างสนับสนุนการเกิดนิ่วสตรูไวท์ ภาวะซิเทรตในปัสสาวะต่ำและภาวะโพแทสเซี่ยมในปัสสาวะต่ำเป็นปัจจัยเสี่ยงทางเมแทบอลิกที่สำคัญในผู้ป่วยโรคนิ่วไตไทย นอกจากนี้ปริมาณปัสสาวะน้อยยังเป็นปัจจัยเสี่ยงที่สำคัญ การรักษาโรคนิ่วไตที่มีประสิทธิภาพควรมีการประเมินภาวะความผิดปกติทางเมแทบอลิก แนะนำการปรับเปลี่ยนพฤติกรรมการรับประทานอาหาร และควรมีการเสริมด้วยยาโพแทสเซี่ยมซิเทรต*

คำสำคัญ : *ภาวะซิเทรตในปัสสาวะต่ำ, ภาวะโพแทสเซี่ยมในปัสสาวะต่ำ, โรคนิ่วไต, ปัจจัยเสี่ยง, ความผิดปกติทางเมแทบอลิก*

Kidney stone has caused considerable morbidity and occasional mortality. In Thailand, the prevalence of kidney stone ranging from 2-16 % has been documented. [1] Once a stone is formed, the probability of the second episode within five to seven years is as high as 50 %.[2] Thus, stone recurrence is a critical problem in stone formers. The management of kidney stone is primarily aimed to remove the stones and reduce the likelihood of their recurrence. To date, frequently used urological approaches are extracorporeal shock wave lithotripsy (SWL) to fragmentize small stones (< 30 mm), percutaneous nephrolithotomy (PCNL) and open stone surgery (OSS). [3-5] Additionally, potassium citrate treatment has been prescribed as prophylactic remedy that is aimed to lengthen the stone-free status. [6]

Various types of kidney stone have been classified according to the primary mineral constituent viz. calcium oxalate, calcium phosphate, magnesium ammonium phosphate (infection stone or struvite), uric acid, and cystine stones. Metabolic abnormalities that cause either an increase of stone promoters (e.g., calcium, oxalate, phosphate, uric acid, cystine) or an decrease of stone inhibitors (e.g., citrate, potassium, magnesium, some urinary proteins) or both in urine have been considered as metabolic risk factors of stone formation.[7] The etiology of these abnormalities varies: some are caused by genetic defects such as primary hyperoxaluria and cystinuria; some develop under extrinsic predispositions, mainly via dietary intake, e.g., hypercalciuria, hypokaliuria, and hypocitraturia; some, however, (about 25 % of stones) are still tagged as idiopathic. [8, 9]

A precise causative factor is hard to be identified in most cases of kidney stone. A family history, history of hypertension, primary hyperparathyroidism, chronic metabolic acidosis and a history of gout have been documented to associate with the higher risk of kidney stone. In addition, anatomical abnormalities of urinary tract such as horseshoe kidney, obstruction of the pelviureteral junction, hydronephrotic renal pelvis or calices, and calyceal diverticulum increase the risk of stone formation. In calcareous stone, metabolic risk factors frequently confronted are hypercalciuria (40-60 %), hyperuricosuria (25 %), hyperoxaluria and hypocitraturia. [8] However, the most common risk factor of all stone types is low urine volume which in turn induces supersaturation of stone promoters enhancing crystal formation and stone development. [10]

The present study is aimed to determine the urinary metabolic risk factors including hypercalciuria, hyperoxaluria, hyperphosphaturia, hyperuricosuria, hypokaliuria, hypocitraturia, and hypomagnesiuria in kidney stone patients and also to investigate the association of these abnormalities with the types of stone.

Materials and Methods

A total of 34 patients with renal stone who underwent the surgical management either PCNL or OSS at Rajavithi Hospital and King Chulalongkorn Memorial Hospital, Bangkok were recruited in the study. Pre-operative 24-hour urine and post-operative stone specimens were obtained from the patients. The patients' residence was classified regarding to regions shown in figure 1. Twenty-four-hour urine samples were obtained from healthy subjects who served as control. Informed consents were accepted from all participants and the research protocol was approved by Ethics

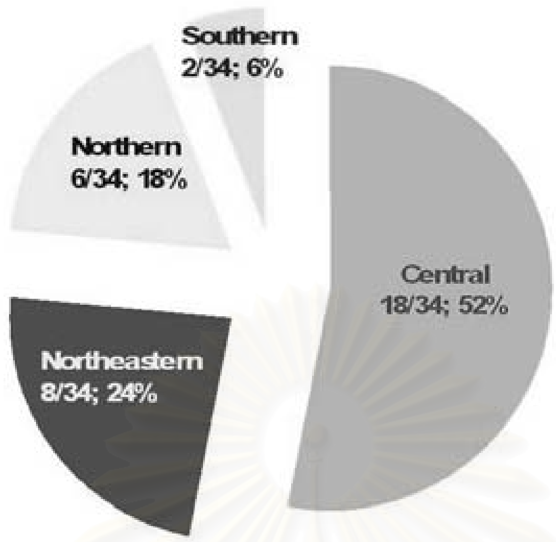

Figure 1. The living habitations of kidney stone participants categorized by region; including central (52%, 18/34), northeastern (24%, 8/34), northern (18%, 6/34) and southern (6%, 2/34) regions.

Committee, Faculty of Medicine, Chulalongkorn University as well as the Ethics Committee of Rajavithi Hospital.

Stone specimens were thoroughly washed with distilled water and incubated at 60^{O}C until dry. Dried stones were grounded into powder and kept at -20^{O}C waiting for analysis. Mineral stone composition was analyzed using Fourier transformed infrared spectrometry (FTIR). Urine samples were determined according to volume, pH and creatinine concentration and aliquots of 100 ml were kept at -20^{O}C for further analysis. Urinary calcium, phosphate and potassium were determined by atomic absorption spectrophotometer. Measurements of oxalate, citrate and uric acid were carried out by specific enzymatic methods. Reference values of urinary metabolic risk factors for kidney stone disease are displayed in Table 1.

Table 1. Reference values of metabolic risk factors predisposing to kidney stone formation.

Urinary risk factors	Cutoff
Hypercalciuria	> 200 mg/d (or > 4 mg/Kg/d)
Hyperoxaluria	> 0.45 mmol/d (or > 40 mg/d)
Hyperphosphaturia	> 0.9 g/d
Hyperuricosuria	> 600 mg/d
Hypocitraturia	< 250 mg/d
Hypokaliuria	< 30 mEq/d
Hypomagnesiuria	< 50 mg/d

Means and standard deviations (SD) were reported for normal distributed data while median and min-max were representative of central tendency of data with skewed distribution. Pie charts were created with Microsoft Excel. Mann-Whitney and Kruskal-Wallis tests were performed to test the difference between continuous data sets of two and three independent groups, respectively. $P < 0.05$ was considered statistically significant. Statistical analysis was accomplished by Stata Version 8 software (College Station, TX).

Results

Metabolic abnormalities in kidney stone and healthy:

As shown in table 2, male-to-female ratios were 0.7 (10/22) and 0.5 (14/20) while means of age

Table 2. General characteristics and metabolic risk factors compared between healthy subjects and kidney stone patients.

Characteristic and Metabolic risk factor	Disease status: Healthy (n=32)	Disease status: Kidney stone (n=34)	P value
Gender (M:F)	10:22	14:20	
Age (year)			
mean (SD)	37.8 (11.0)	43.6 (13.3)	
24-hr urine volume			0.006*
(ml) mean (SD)	2142.5 (773.0)	1584.7 (806.5)	
median (min-max)	2135 (810.0-4050.0)	1850 (180.0-3190.0)	
Urine pH			0.172
mean (SD)	6.4 (0.3)	6.3 (0.7)	
median (min-max)	6.4 (5.8-6.9)	6.3 (5.3-9.1)	
Creatinine (g/d)			0.078
median min-max	0.8 (0.4-2.2)	0.7 (0.1-2.6)	
Calcium (mg/d)			0.069
median (min-max)	66.7 (1.2-216.8)	39.6 (1.3-218.0)	
Oxalate(mmol/d)			0.748
median (min-max)	0.0800 (0.0010-0.8300)	0.1200 (0.0003-1.2400)	
Phosphate (g/d)			<0.001*
median (min-max)	0.66 (0.21-1.43)	0.34 (0.04-1.08)	
Uric acid (mg/d)			0.700
median min-max	444.3 (98.9-1198.9)	439.3 (41.4-1202.2)	
Citrate (mg/d)			<0.001*
median (min-max)	262.2 (30.7-552.9)	45.9 (1.0-235.8)	
Potassium (meq/d)			<0.001*
median (min-max)	28.4 (11.3-86.7)	15.8 (2.5-66.0)	
Magnesium (mg/d)			0.069
median (min-max)	54.7 (1.8- 117.0)	37.1 (1.1-101.8)	

*: statistical significance (Mann-Whitney test, $P < 0.05$)

were 43.6 ± 13.3 and 37.8 ± 11.0 years old for kidney stone patients and control subjects, respectively. The volume of 24-hour urine of stone patients was significantly smaller than the healthy controls (P = 0.006) whereas excretory creatinine (P = 0.078) and urinary pH (P = 0.172) between these two groups were not statistically different. Unpredictably, the excretory levels of calcium (P = 0.069), oxalate (P = 0.748), and uric acid (P = 0.700) were statistically equivalent between the case and the control groups. Urinary phosphate excretion was considerably higher in healthy subjects than in stone patients (P < 0.001). Excretion levels of stone inhibitory substances, citrate (Figure 1) and potassium were drastically lower in renal stone patients than those found in healthy subjects (P < 0.001 for both). In contrast, level of urinary magnesium was rather similar among the studied groups (P = 0.069) (Table 2).

Metabolic abnormalities, which were classified regarding to cutoff values shown in

Table 3. The frequency of metabolic abnormalities found in kidney stone patients compared to healthy controls.

Metabolic abnormality	Disease status		P value
	Healthy (n=32)	**Kidney stone (n=34)**	
Hypercalciuria			1.000
- No	31 (96.9%)	32 (94.1%)	
- Yes	1 (3.1%)	2 (5.9%)	
Hyperoxaluria			0.663
- No	28 (90.3%)	31 (91.2%)	
- Yes	3 (9.7%)	3 (8.8%)	
Hyperphosphaturia			0.297
- No	26 (81.3%)	31 (91.2%)	
- Yes	6 (18.8%)	3 (8.8%)	
Hyperuricosuria			0.322
- No	22 (68.7%)	27 (79.4%)	
- Yes	10 (31.3%)	7 (20.6%)	
Hypocitraturia			<0.001*
- No	18 (56.3%)	0 (0.0%)	
- Yes	14 (43.8%)	34 (100.0%)	
Hypokaliuria			0.024*
- No	15 (49.6%)	7 (20.6%)	
- Yes	17 (53.1%)	27 (79.4%)	
Hypomagnesiuria			0.145
- No	17 (51.3%)	12 (35.3%)	
- Yes	15 (46.9%)	22 (64.7%)	

*: statistical significance (χ^2-test, P < 0.05)

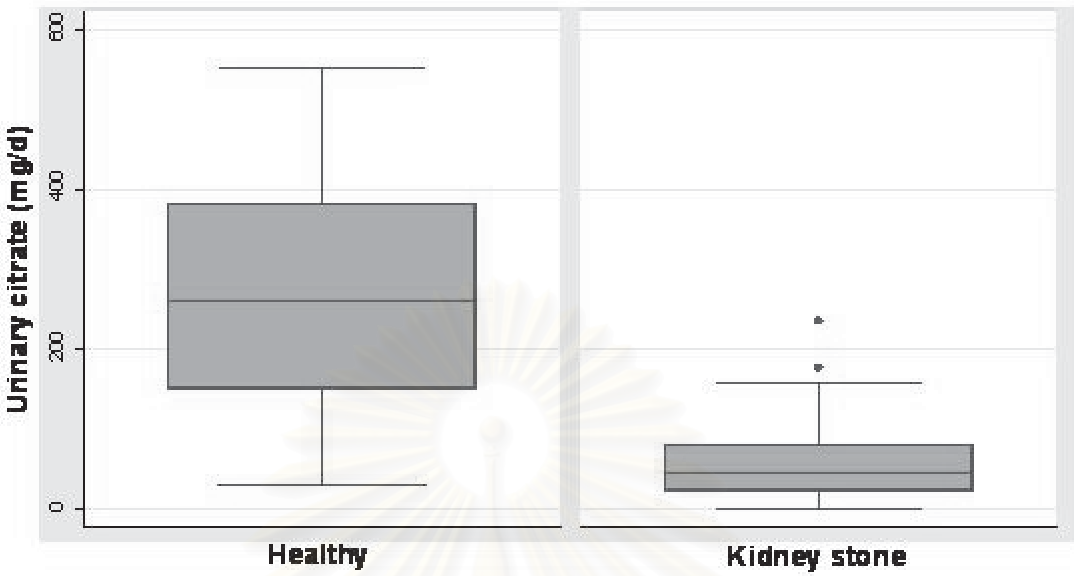

Figure 2. Box-Whisker plot shows the comparison of urinary citrate daily excretion between healthy and kidney stone subjects. A significant difference using Mann-Whitney test was revealed ($P < 0.001$).

Table 1, included hypercalciuria, hyperphosphaturia, hyperoxaluria, hyperuricosuria, hypocitraturia, hypokaliuria, and hypomagnesiuria were assessed in kidney stone patients when compared to healthy subjects. The frequencies and percentages of metabolic disorders in renal stone and the healthy controls are shown in Table 3. Proportions of hypercalciuria ($P = 1.000$), hyperoxaluria ($P = 0.663$), hyperphosphaturia ($P = 0.297$), and hyperuricosuria ($P = 0.322$) found in kidney stone patients were not significantly different from those observed in healthy controls. Hypocitraturia ($P < 0.001$) and hypokaliuria ($P = 0.024$) were significantly associated with renal stone disease. Interestingly, hypocitraturia was presented in all stone patients (100 %). Hypomagnesiuria however observed in stone and control subjects was not statistically different ($P = 0.145$).

Metabolic risk factors in various stone types:

Mineral constituent of stone was analyzed by FTIR technique. Three types of stone were classified, namely: calcium oxalate (CaOx), magnesium ammonium phosphate (MAP), and uric acid (UA) stones. The major type of stone observed in the present study was CaOx stone (67 %, 23/34) while prevalence of MAP (18 %, 6/34) and UA (15 %, 5/34) stones was rather similar (Figure 3).

Urinary pH and levels of stone promoters and their inhibitors were compared among the three stone types. Urinary pH was statistically different among three types of stone groups ($P = 0.003$). Urinary pH of patients with MAP was higher than those with CaOx and UA. In MAP stone patients, urinary pH ranged from slightly acidic to considerably basic (pH 6.55-9.10) whereas it was more acidic (pH < 6.0) in UA stone patients. Association of stone promoter profiles

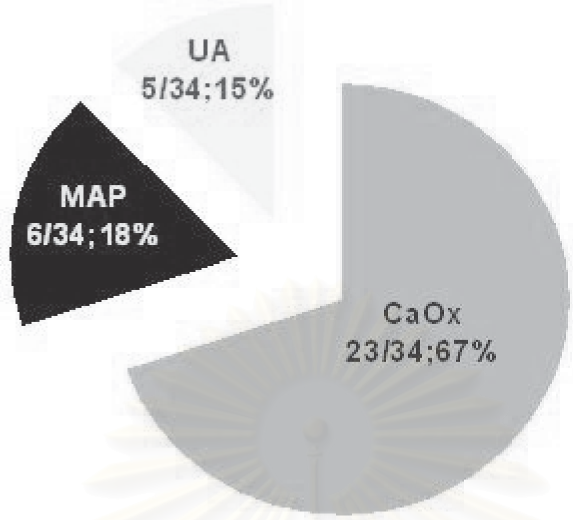

Figure 3. Frequency and percentage of stone types identified among kidney stone patients. Three types of stone were classified according to the principal amount of mineral constituent viz. calcium oxalate (CaOx), magnesium ammonium phosphate (MAP), and uric acid (UA) stones

(calcium, oxalate, phosphate, and uric acid) with stone types was not revealed (P > 0.05 for all). However, a trend of higher excretion of calcium and phosphate was observed in CaOx and MAP stone patients, respectively. Also, the excretory profiles of stone inhibitors (citrate, potassium, and magnesium) were not related to the types of stone (P > 0.05 for all).

Discussion

Metabolic risk factors of kidney stone and of particular stone type were evaluated in the present study. The data clearly demonstrated that low urine excretion and reduction of stone inhibitors, especially citrate and potassium, were important risks of calculi development.

A low urine volume has been well known as an important risk factor in urinary stone formation and a high fluid intake is the oldest existing treatment for kidney stones.[10, 11] A high water intake causes an increase in urine volume consequently results in a marked reduction in saturation of lithogenic substances producing favorable effects on the crystallization while the activity of natural inhibitors is not altered. Borghi *et al.* demonstrated a decrease in CaOx supersaturation and an increase of the permissible increment in oxalate in both stone formers and normal subjects after water load emphasizing the protective effect of water in stone formation. [12] Thereby, a high intake of fluids, especially water, is still the most powerful and certainly the most economical means of prevention of nephrolithiasis.[11] On average, water excretion of our stone patients was approximately 1500 ml per day, whereas healthy subjects excrete over 2000 ml per day. Physicians should encourage stone patients to consume water at least 2000 ml per days or 8-10 glasses (250 cc in size) of water in order to prevent the recurrence of calculi.

Basically, hypercalciuria (40-60 %) is the most common metabolic abnormality in calcareous stone patients, which results from various mechanisms including increased gastrointestinal absorption (absorptive hypercalciuria), impaired renal tubular reabsorption of calcium (renal hypercalciuria) and increased resorption of the bone (resorptive hypercalciuria). Absorptive hypercalciuria is very common while renal and resorptive hypercalciuric forms are accounted for 2 % and 5 % of recurrent stone patients, respectively. A recent study reported a high prevalence of hypercalciuria (74 %) in Brazilian stone populations. [13] The present study found that urinary calcium excretion in renal stone patients was not significantly different from healthy controls; moreover, hypercalciuria was observed only 2 out of 34 stone patients (5.9 %). These obviously indicated that elevated excretion of calcium was not a main metabolic risk factor of our stone patients. Also, these may suggest a low ingestion of high calcium-containing foods in Thai patients.

No difference of urinary calcium level among various stone types was also found in this study and the average calcium levels in all groups were < 50 mg/d (Table 4). Trinchieri *et al.* reported excretory level of calcium over 200 mg/d (about 4-fold higher than that of our data) in calcium oxalate stone patients and the calcium level was significantly lower in patients with calcium oxalate stone mixed with uric acid or ammonium urate. [14] The findings imply that an elevation of stone promoter is a key causative factor for stone formation in western patients but this is not found in Thai stone patients; it is perhaps due to stone inhibitor depletion.

Oxalate is a potent stone promoter and it is per se capable to induce oxidative stress and consequently renal tubular damage as well as inflammation. [15] In supersaturated urine, oxalate rapidly complexes with calcium forming an insoluble calcium oxalate crystal, a primary constituent of calculi. Hyperoxaluric state is caused by three main mechanisms: increased oxalate ingestion, increased intestinal absorption due to bowel diseases, and genetic inborn error of oxalate metabolism (primary hyperoxaluria). The former directly involves the dietary habit. Dietary oxalate contributes to about 50 % of the urinary oxalate. [16] High consumption of spinach, rhubarb, beets, chocolate, nuts, tea, wheat bran, strawberry, and soya foods are recognized to increase urinary oxalate concentration. Supplementation of vitamin C increases the endogenous synthesis of oxalate creating hyperoxaluric condition. [17, 18] In contrast, dietary calcium influences the bioavailability of ingested oxalate restricting intestinal oxalate absorption and thus preventing hyperoxaluria. [16] At present, various lines of evidences indicate that hyperoxaluria is associated with dietary vitamin C but it is inversely related to calcium intake.[19] However, the current data did not show any significant amount of higher oxalate excretion in kidney stone patients (Table 2) and the proportion of hyperoxaluria was also not statistically different from those of healthy subjects (Table 3). These suggested that hyperoxaluria was not a primary risk factor of our stone patients. Since a trend of higher excretion of oxalate in the stone group was observed, a restriction of high oxalate-containing foods is recommended.

Table 4. Comparison of metabolic profiles between various stone types.

Variable	Stone type CaOx	MAP	UA	P-value
Number of cases (n)	23	6	5	
Urinary pH				0.003*
Median	6.20	6.86	5.44	
min-max	5.54-7.47	6.55-9.10	5.25-5.99	
Stone promoters				
Calcium (mg/d)				0.228
Median	46.50	12.83	26.98	
min-max	3-217.96	9.26-171.62	1.26-94.43	
Oxalate (mmol/d)				0.131
Median	0.110	0.160	0.050	
min-max	0.003-0.861	0.003-0.537	0.007-0.136	
Phosphate (g/d)				0.789
Median	0.32	0.40	0.33	
min-max	0.04-1.08	0.15-0.96	0.16-1.05	
Uric acid (mg/d)				0.951
Median	455.40	446.97	330.82	
min-max	41.40-1202.20	104.00-1087.80	145.30-839.20	
Stone inhibitors				
Potassium(mEq/d)				0.486
Median	13.67	20.13	26.60	
min-max	2.52-63.58	7.2-66.03	7.56-37.74	
Citrate (mg/d)				0.351
Median	58.44	46.71	24.93	
min-max	2.92-235.78	0.97-176.44	10.44-81.50	
Magnesium(mg/d)				0.942
Median	37.05	43.89	25.70	
min-max	4.39-100.86	1.14-101.44	6.09-101.84	

*: statistical significance (Kruskal-Wallis test, $P < 0.05$)

Abbreviations: CaOx; calcium oxalate stone, MAP; magnesium ammonium phosphate stone, UA; uric acid stone

Hyperuricosuria increases a risk for both uric acid and calcium stones. Uric acid is the end product of purine metabolism. Therefore high ingestion of purine-rich diets (exogenous source) and increased cell destruction and turnover (endogenous source) increase the urinary uric acid concentration producing hyperuricosuria. High protein intake leading to metabolic acidosis also causes hyperuricosuria and increases risk of stone formation. [20, 21] Hyperuricosuria of 33 % is a reported risk factor for calcium oxalate stone formation in Japanese patients [22] while study in Brazilian urolithiasis patients reports hyperuricosuria of around 20 %. [13] Our data found hyperuricosuria of 21 % in renal stone patients which corresponded to other regions. However, the similar proportion of hyperuricosuria (31 %) was observed in healthy subjects. This suggested that a concerted action with additional risk factors or metabolic abnormalities is required for achieving stone formation.

Hypocitraturia or low urinary citrate excretion is a common disorder occurring in >50 % of patients with nephrolithiasis [23, 24] and known as an ominous sign for recurrent nephrolithiasis. [25, 26] Citrate, as a stone inhibitor, forms a soluble complex with calcium that inhibits the crystallization hence it reduces the likelihood of stone formation. Generally, citrate excretion is lower in men than women [27, 28], which is one of the reasons for higher incidence of kidney stone in men. The amount of citrate excretion is mainly depended upon dietary intake. [29] A recent study, however, suggests a genetic influence on citrate excretion likewise seen on calcium excretion. [30] Intracellular acidosis (often from chronic metabolic acidosis and renal tubular acidosis), acidic diets (animal protein-rich diets) and hypokalaemia (also hypokaliuria) decrease the excretion of urinary citrate. Citrus fruits such as orange, grapefruits, apple and lemon are the main exogenous source of citrate and many studies demonstrate the beneficial effect of these fruits on recurrent stone prevention. [29, 31-33] In Thailand, kidney stone is a common disease of rural communities especially in the northeastern region where hypocitraturia and potassium deficiency (indicated by hypokalaemia and hypokaliuria) are predominant abnormalities. [34] Consumption of high carbohydrate and low fat diets, in which are low in potassium content, causes chronic potassium depletion which leads to chronic metabolic acidosis and intracellular acidosis, consequently increases the reabsorption of urinary citrate and thus producing hypocitraturic state. [35] The present study found the prevalence of hypocitraturia (100 %) and hypokaliuria (79 %) was greatly higher in stone patients than healthy subjects (Table 3) and the data were corresponded with previous studies done in northeastern region. Therefore, it can be stated that diminution of stone inhibitor particularly citrate and potassium was a main risk factor of stone patients in Thailand. However, hypocitraturia and hypokaliuria proportions are rather high in healthy people. Modification in dietary habit is necessary to break up the potential of stone formation.

The highest prevalence of calcium oxalate stones and relatively high prevalence of uric acid stones were found in the present study (Figure 3). They corresponded to our previous study in conducted Udon Thani Hospital. [36] This indicates certain pattern of stone distribution in Thailand. In deed, the stone figure is similar to the distribution of stone type worldwide. [37, 38]

Our data showed that the metabolic profiles compared between CaOx, MAP and UA stones were not significantly different from one another (Table 4). This suggested that metabolic evaluation was not valid for predicting stone type. Only urinary pH showed significant difference among the three types of stones. Acidic urine preferred to initiate UA stone formation whereas relatively basic urine promoted MAP crystallization. Because of the pKa for dissociation of the N_9 proton of uric acid is 5.35, urinary pH of < 5.5 is considered as an important risk factor for UA stone. Low excretion of ammonia is partly contributed to low urinary pH. [39, 40] Low urinary pH and UA stone are common in gout patients, diabetes mellitus and metabolic syndrome, probably as a result of insulin resistance that may reduce renal ammonia excretion. [41] Restriction in purine-containing foods as well as maintenance the urine pH at > 6.0 (by mean of potassium alkali administration, for instance) are crucial for prevention and management of UA stone.

MAP stone associated with the alkali urine was found in this study. Literally, urinary infection with urea splitting-microorganisms such as *Proteus*, *Klebsiella*, *Serratia*, *Pseudomonas*, *Staphylococcus* and *Mycoplasma* creates alkali urine and it is associated with MAP (or struvite) stone formation. [42] Thus, elimination of infectious agents is mandatory for the management of MAP stone.

In conclusion, calcareous stone is still the most prevalent stone and uric acid stone is steadily increased. This may be due to the change in dietary habit and viability of food variety. Basic urinary pH is a risk factor of struvite stone in contrast to uric acid stone prefers acidic urine pH. The major metabolic risk factor of Thai renal stone patient is not the elevation of stone promoters but it is certainly the reduction of stone inhibitor particularly hypocitraturia and hypokaliuria. Low urine excretion is still a critical stone risk. Modification in alimentary and behavioral habits to consume water as well as diets with high citrate and potassium contents sufficiently is necessary to reduce the potential of stone formation.

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