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Original article

Crystalline composition and etiologic factors of kidney stone in Thailand : update 2007

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Objective: The etiology of kidney stone is multifactorial including environmental, behavioral and genetic. Insights about predisposing causes and mineral composition are mandatory for better management of kidney stone disease. The present hospital-based study aims to explore the mineral constituents and etiologic risks of kidney stones in Thai patients from the four geographic regions of the country.

Method: Two hundred and fifty six kidney stone patients from four geographic regions of Thailand, including the northeastern (n=103), the northern (n=81), the central (n=47) and the southern (n=25) were recruited in this study. Of these, 144 patients completed the food frequency questionnaire to assess the kidney stone risk. Mineral composition of stones were analyzed by Fourier transformed infrared spectrometry.

Results: Kidney stone frequently affected peoples aged 40-49 years. Only 31.9 % of patients had a positive family history of renal stone. Calcium oxalate (CaOx) stone was the most prevalent type (73.8 %). Uric acid (UA) stone was found in 16.0 % commonly affected peoples aged 60-70 years. Mixed stones, notably CaOx mixed with calcium phosphate (CaP), were more prevalent than pure stones. The food frequency questionnaire data showed that 59.7 % of stone patients consumed less than two liters of water per day. Low intakes of fruits and vegetables were notably present. In contrast, high consumption of rice was observed in over 65 % of stone patients.

Conclusion: CaOx mixed with CaP was the most prevalent stone type. UA stone was more likely to occur in the elderly. Kidney stone patients were found to consume less-than-adequate amounts of water, food high in carbohydrates, along with low consumtion of fruits and vegetables. These dietary habits might be risk factors in stone development among the Thai population.

Keywords: Dietary risk factor, family history of renal stone, kidney stone risk factor, nephrolithiasis, stone composition.

Kidney stone disease is a longstanding medical illness and still a common public health problem. It affects up to 20 % of the general population worldwide [1]. In the United States, up to 12% of men and 6 % of women will develop a renal stone at some point in life [2]. In Thailand, the highest prevalence (16.9 %) was reported in the Northeast provinces [3], while in Middle Eastern countries, the lifetime prevalence of kidney stone is even higher [4]. Kidney stone usually recurs and it poses difficulty in management and burdensome medical costs [5]. Recurrence rates as high as 50 % in 10 years have been documented [6].

Calcareous stone is the most common type of kidney stone disease. It accounts for more than 80 % of all stones. The primary chemical complexes are calcium oxalate (CaOx) and calcium phosphate (CaP) [7]. Uric acid (UA) stone represents about 4.5–23 %

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and the other less frequent types of kidney stones are magnesium ammonium phosphate (MAP) or struvite stones, ammonium urate stones, cystine stones, xanthine and other miscellaneous stones [4].

The etiology of kidney stone is multifactorial. It includes both intrinsic factors such as demographic (age, gender and race), anatomic and genetic aspects, and extrinsic factors such as geographic predilection, climate, lifestyle pattern as well as dietary habits. During the past few decades, the prevalence of kidney stones in both males and females markedly increased in industrialized countries [7]. This is presumably due to changes in lifestyle and dietary habit. Understanding how the stone forms in vivo will herald means to prevent its development.

Supersaturation of urinary lithogenic promoters such as calcium, oxalate, phosphate and uric acid are considered as the risk factors of renal stone formation. On the other hand, a decreased urinary concentration of stone inhibitors such as citrate, potassium and magnesium is also a critical risk. The urinary levels of these stone modulators are greatly influenced by diet [8-10].

In the present study, we investigated the mineral composition and causative risk factors of kidney stone in patients living in different regions of Thailand.

Materials and methods

The present study was a hospital-based cross-sectional study. Patients who underwent upper urinary tract stone (UUTS) operations at hospitals between March 2005 and December 2006 were archived. Two hundred and fifty six kidney stone specimens were collected from main hospitals in four geographic regions of Thailand (**Fig. 1**). In the northeastern (NE), 103 stones were collected from Udon Thani Hospital. In the northern (N), 81 specimens were obtained from Maharaj Chiangmai Hospital and Mae Sot Hospitals. In the central (C), 47 kidney stones were from Rajavithi Hospital and King Chulalongkorn Memorial Hospital. In the southern (S), the 25 specimens were from Songklanagarind Hospital.

To analyze mineral constituents of stone, the stone was washed, dried overnight at 60°C, ground into powder and kept at -70°C until analysis of the crystalline composition of stones with Fourier transform infrared spectroscopy (FTIR).

A food frequency questionnaire (FFQ) was devised to assess dietary risk factors for nephrolithiasis. Of 256 patients, 144 voluntarily participated in the interview and completed the FFQ. Patients were asked to recall all food they consumed during 7 consecutive days prior to the day of interview.

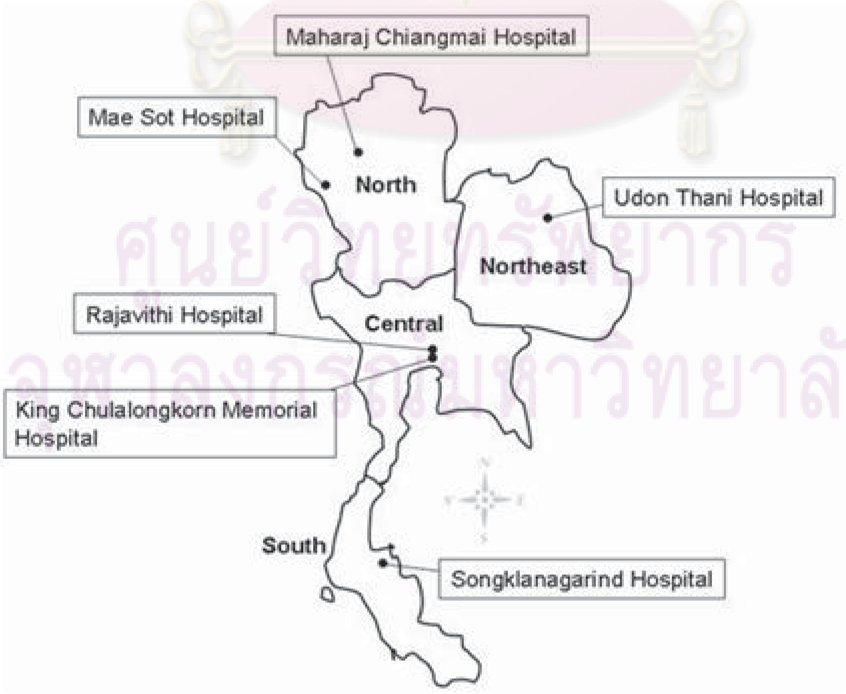

Fig. 1 Four geographic regions of Thailand and the locations of 6 hospitals used to recruit the kidney stone patients.

Daily intake of water was estimated based upon the question "How many glasses of water do you drink per day?" and a demonstration of volume of a glass of water (equals to 250 ml). Water intake less than 2 liters (8 glasses) per day was considered a risk factor of nephrolithiasis.

The daily consumption of particular nutrients including carbohydrates (mainly from rice), animal proteins, vegetables and fruits were estimated. The amount of daily food intake was expressed as serving portions per day. A serving portion of rice used in the present study is equal to one serving spoon (approximately 60 grams). A serving of animal proteins was about one ounce (approximately 30 grams). A serving portion of vegetables was equal to 60 grams, or one serving spoon, whereas a serving of fruits was equal to two pieces of fresh fruits or a three-fourth cups of fruit juice.

The data were expressed as mean±SD. The difference of means of patients' age among regions was tested by one way ANOVA followed by the Bonferroni test. Two-sample tests of proportion were carried out to test the difference of proportion of patients who were exposed to stone risk factors versus the proportion of patients who were not. All statistical tests were 2-tailed analysis computed by Stata software version 8.0 (Collage Station, TX). P value less than 0.05 was considered statistically significant.

Results

Stone composition analysis

Two-hundred and fifty-six kidney stone patients participated in the present study. They were categorized into four geographic regions according to their native residence (**Table 1**); the northeastern (n=103), the northern (n=81), the central and the southern (n=25). Overall, the ratio of male-to-female was 1.2:1 (54 % versus 46 %). Mean±SD of age of total cases was 49±14 years (range, 16-88 years). On average, age of northeastern (46±13 years) patients was significantly lower than those from southern (56±13 years, P=0.008). A high occurrence of kidney stones was observed in patients aged between 30-69 years with the majority between 40-49 years (**Fig. 2**).

Table 1. Demographic data of kidney stone patients.

Characteristics	Total	Geographic regions			
		NE	N	C	S
Number of patients	256	103	81	47	25
Gender					
Male (%)	138 (53.9)	50 (48.5)	56 (69.1)	18 (38.3)	14 (56.0)
Female (%)	118 (46.1)	53 (51.5)	25 (30.9)	29 (61.7)	11 (44.0)
Age (years)					
Mean SD	49 14	46 13*	49 14	49 14	56 13*

*Bonferroni test (NE vs. S), P = 0.008.
NE: northeastern, N: northern, C: central, S: southern.

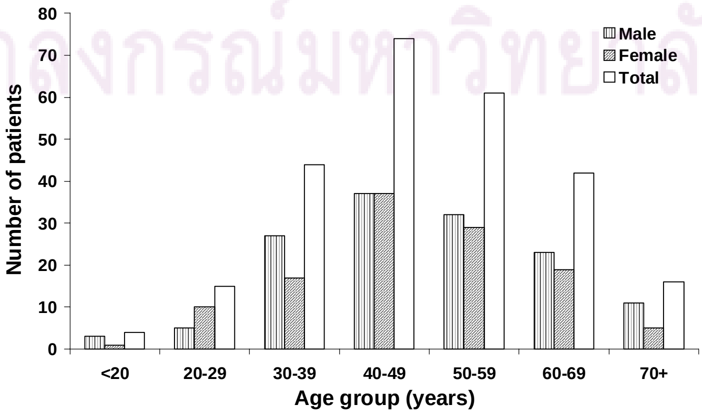

Fig. 2 Age and sex distribution of 256 patients with kidney stones in all geographic regions of Thailand.

The results of stone composition analysis with FTIR showed that 103 patients (40.2 %) were afflicted with pure stones, whereas 153 patients (59.8 %) had mixed stones. Pure CaOx and pure UA stones were found, respectively, 21.1 % (54/256) and 14.1 % (36/256) of all stone types, but they accounted for approximately 90 % of the pure stones (**Table 2**). CaOx mixed with CaP was the main stone type and accounted for 80 % of the mixed stones group. Pure MAP stone (also known as struvite or infection stone) was found in only 3.1 % (8/256) of all stone types. Five out of 256 (2.0 %) accounted for the pure CaP stones.

When stone types were classified based upon the major mineral constituent of stones, CaOx, UA, CaP and MAP accounted for 73.8 % (189/256), 16.0 % (41/256), 5.5 % (14/256) and 4.7 % (12/256), respectively. CaOx stones had the highest prevalence in all regions. There was no statistical difference in the frequency distribution of stone constituents among the 4 geographic regions with respect to either the pure stone or mixed stone groups. It is noteworthy that the prevalence of uric acid stone tended to be higher in the central and the southern although not statistically significant.

The age distribution of patients compared among stone types is shown in **Fig. 3**. The age peak of patients with the CaOx stone was in the fifth decades whereas those with UA stone were between 60-69 years. The sex distribution of patients (**Fig. 4**) harboring each type of stones was similar except for UA stone patients in which there was a male preponderance (66 % in male versus 34 % in female, $P=0.004$).

Risk factor assessment

Of 256 kidney stone patients, 144 completed the interview to assess the kidney stone risk factors. The proportion of patients with the first (51 %) and recurrent (49 %) stone episodes were not significantly different ($P=0.637$). Forty-six out of 144 patients (32 %) had a family history of kidney stone disease.

To determine the impact of nutritional status on stone occurrence, body mass index (BMI) was used and categorized into two groups, patients with BMI <23 and those with BMI ≥ 23 representing overweight and obese in Asian adults, respectively. Proportion of overweight and obese patients was higher than proportion of patients with BMI < 23 although the significant difference was not observed ($P=0.059$).

Table 2. Primary constituents of kidney stones obtained from patients in each region of Thailand.

Stone composition	All regions		Geographic regions							
			NE		N		C		S	
	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%
n	**256**		**103**		**81**		**47**		**25**	
Pure stones	**103**	**40.23**	**37**	**35.92**	**29**	**35.80**	**24**	**51.06**	**13**	**52.00**
CaOx	54	21.09	19	18.45	18	22.22	13	27.66	4	16.00
UA	36	14.06	12	11.65	11	13.58	8	17.02	5	20.00
CaP	5	1.95	2	1.94	0	0	1	2.13	2	8.00
MAP	8	3.13	4	3.88	0	0	2	4.26	2	8.00
Mixed stones	**153**	**59.77**	**66**	**64.08**	**52**	**64.20**	**23**	**48.94**	**12**	**48.00**
CaOx+CaP	122	47.66	52	50.49	46	56.79	15	31.91	9	36.00
CaOx+UA	12	4.69	6	5.83	3	3.70	2	4.26	1	4.00
CaOx+others	8	3.13	4	3.88	2	2.47	1	2.13	1	4.00
Others	11	4.30	4	3.88	1	1.23	5	10.64	1	4.00
Stone types regarding to the major crystalline component										
CaOx	189	73.83	77	74.76	68	83.95	29	61.70	15	60.00
CaP	14	5.47	7	6.80	1	1.23	3	6.38	3	12.00
UA	41	16.02	13	12.62	12	14.81	11	23.40	5	20.00
MAP	12	4.69	6	5.83	0	0	4	8.51	2	8.00

CaOx: calcium oxalate, UA: uric acid, CaP: calcium phosphate, MAP: magnesium ammonium phosphate (infection stone), other mix stone type (xanthine, ammonium urate and calcium carbonate), NE: northeastern, N: northern, C: central, S: southern.

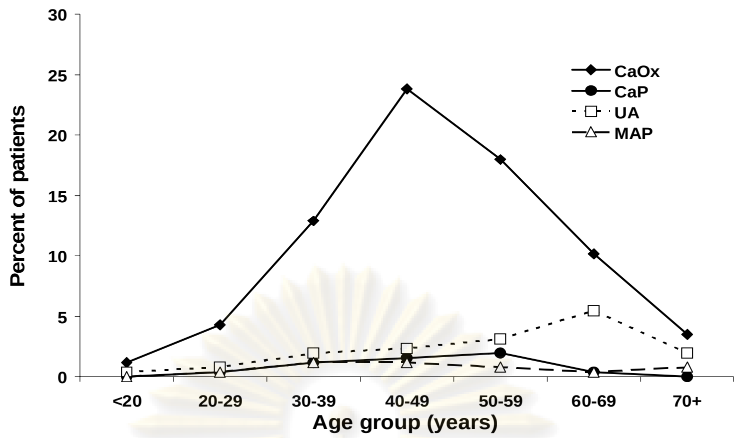

Fig. 3 Percent of kidney stone patients by age group for each stone type in Thailand. CaOx: calcium oxalate, CaP: calcium phosphate, UA: uric acid, MAP: magnesium ammonium phosphate (infection stone).

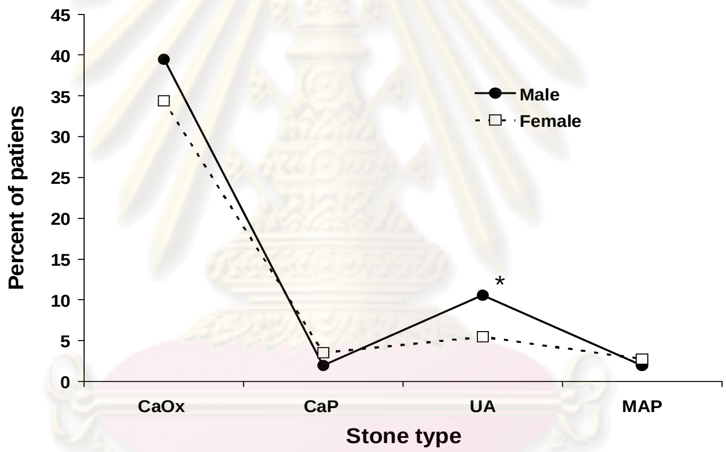

Fig. 4 Percent of kidney stone patients by stone types for male and female in Thailand. * indicates a significant P-value of proportion test in patients with UA stone (P = 0.004). CaOx: calcium oxalate, CaP: calcium phosphate, UA: uric acid, MAP: magnesium ammonium phosphate (infection stone).

FFQ assessment revealed that 60 % of patients (86/144) consumed less than 2 liters of water per day. This was significantly greater than patients who consumed water $\geq$ 2 liters a day (P=0.001) (**Table 3**). The amount of daily food consumption estimated from FFQ was shown in **Fig. 5**. The data showed that majority of kidney stone patients consumed rice at five or more servings a day. In contrast, about 45 % of patients consumed two servings of animal protein per day. About 80 % of cases, daily consumption of vegetables and fruits were not greater than two serving a day. Interestingly, 32 out of 144 patients (22 %) consumed no fruits within the recalled period of interview.

Discussion

Kidney stone disease is common in the rural communities of Northeastern Thailand [3, 16]. We updated the mineral composition and risk factors of kidney stone in Thailand. Calcareous stone was the predominant stone type and a high prevalence of uric acid stone was observed. Mixed stones notably CaOx mixed with CaP were more prevalent than the pure stones. Calcium stones frequently affected peoples aged between 40-49 years while age at risk of UA stone was 60-69 years. Significantly more men were afflicted with UA stone more than women. Most of stone patients had a negative family history of renal stone. FFQ data showed that most of stone patients

Table 3. Percentage of stone recurrence and risk factors in 144 kidney stone patients.

Variable/ Risk factor	Frequency (n=144)	Percent	P value
Stone recurrence			0.637
First episode	74	51.39	
Recurrence episode	70	48.61	
Family history			<0.001*
Negative	98	68.06	
Positive	46	31.94	
Nutritional status			0.059
BMI < 23.0	64	44.44	
BMI ≥ 23.0	80	55.56	
Water intake			0.001*
< 2 liters/day	86	59.72	
≥ 2 liters/day	58	40.28	

** indicates statistical significance of proportion test (P < 0.05).*
BMI: body mass index

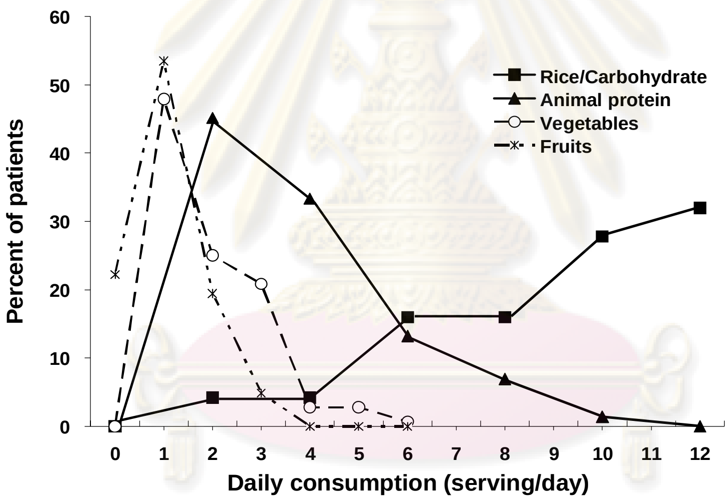

Fig. 5 Daily intake of rice, animal proteins, vegetables and fruits in 144 renal stone patients. The serving portion was derived from food frequency questionnaire (FFQ).

consumed water less than 2 liters per day. Low intakes of fruits and vegetables were frequently present. In contrast, high consumption of rice was observed in over 65 % of stone patients.

Our study showed that CaOx stone was the most prevalent kidney stone type (74 %), similar to the reports of stone distribution worldwide. In Europe, CaOx stone was reported 61 %, [11, 12] while the greater prevalence was found in Okinawa (82 %), Japan [13] and in India (93 %) [14]. Most studies found that pure stones were more prevalent than the mixed ones. In contrast, our data revealed that mixed stones, chiefly CaOx mixed with CaP, were more common. CaP crystals are formed in the proximal tubules of the nephron, where urine is alkaline (pH > 7.0), while CaOx crystals are formed only when the urine reaches the distal tubules and collecting ducts, where it is slightly acidic (pH 5.5-6.4). Early-formed CaP crystals can nucleate CaOx in metastable urine at the later nephron segments; thus, heterogeneous nidus is predominantly formed [15]. This might be the explanation for the high prevalence of CaOx cohered with CaP.

According to a study in 1983, a low prevalence of UA stone (3 %) was reported in Northeastern Thailand [16]. In the present study, a relatively high prevalence of UA stone (16 %) was found, especially in the central and southern regions. It is interesting that the peak age of patients with UA stones (60-69 years) is about 20 years, older than that of patients with CaOx stones (40-49 years). Hyperuricosuria is a cause of UA stone, which is underlying by various mechanisms. High consumption of high-purine or high-protein diets directly contributes to hyperuricosuria [17]. Hypocitraturic state also increases a risk of UA stones. Our previous study found that approximately 80 % of Thai kidney stone patients presented with hypocitraturia and the main causes of this metabolic abnormality were low intake of potassium and citrus fruits, as well as high intake of carbohydrates [18-21]. These dietary habits may be a risk factors for UA stone in Thai patients.

The higher prevalence of UA stone in the central and southern regions than in the northeastern and the northern parts was revealed. This might be due to the similarity of diet among central and southern peoples that more frequently consume high-purine diets than peoples in the northeastern and northern regions. However, other causes of hyperuricosuria and hypocitraturia, such as genetic defect and other underlying diseases, can not be ruled out.

The range of age incidence of kidney stone patients in this study was between 30-59 years; this is consistent with other reports [11-13]. However, the age onset of kidney stone in the southern group was significantly delayed about 10 years older than the patients from the northeastern region (**Table 1**). This finding might be attributed to differences in climate and dietary components between the northeastern and southern regions. In the Northeastern region, there are three seasons, the hot, rainy and cool whereas in the southern part only two seasons exist; the hot (and humid) and the rainy (and very humid). Since traditional dietary habit and occupation between the northeastern and the southern are distinctively different, patterns of diet as well as work activity may be other causes.

Familial risk of urolithiasis has been reported in about 16-37 % of patients studies. People with family history of kidney stones are at higher risk than those without [22, 23]. Our data showed a consistent figure with a positive family history of 32 %. This implies that the influence of extrinsic factors superimposes on the intrinsic causes [24]. Moreover, it should be noted that the occurrence of kidney stone within the family may be promoted by living in the same environment along with having the similar dietary habits, lifestyles and activities. This emphasizes the contribution of extrinsic factors on stone formation. Nevertheless, genetic susceptibility of renal stone development has been suggested [23, 25, 26].

Dietary factors are an important risk for kidney stone formation [10, 27]. High fluid intake is associated with a lower risk of kidney stone development in both men and women [31]. High intake of animal proteins increases urinary excretion of acid ash (and thus lowers urine pH), calcium, phosphate, oxalate ,uric acid and decreases urinary citrate excretion [28, 29]. Our previous data demonstrated that kidney stone patients in the Northeastern Thailand who consumed high-carbohydrate (with low potassium content) and low-fat and normal-protein food had low urinary excretion of citrate [19,20]. In addition, the stone patients preferred to eat local high-oxalate vegetables.

The US Department of Agriculture Food Pyramid Guide is as follows: 5-8 servings of complex carbohydrate (5-8 ounces), a serving of meat (about 2-3 ounces) as well as 2-3 servings of fruits and 2-3 servings of vegetables. The healthy diet emphasizes fruits, vegetables, whole grains, and fat-free or low-fat milk and milk products.

The present study found that high carbohydrate consumption, low fruit and vegetable intake were frequently present in the stone patients (**Fig. 4**). A main form of carbohydrate ingested by our patients was polished rice which had high glycemic index property but low potassium content. The consumption of high glycemic index carbohydrate results in increased urinary calcium excretion [30, 31]. Although the precise mechanism is still subtle, this effect has been believed to be mediatel partly via insulin. Low potassium intake also increases a risk of stone formation [32].

It is well recognized that oxidative stress mediates the pathogenesis of kidney stone and the foremost sources of dietary antioxidants are vegetables and fruits. High consumption of vegetables and fruits increases antioxidative force in the body and diminishes the stone forming potential [33, 34]. We speculate that the high ingestion of polished rice and low consumption of vegetables and fruit in our stone patients might contribute to hypokaliuric and hypocitraturic phenotypes which are prevailing metabolic risk factors of kidney stone in Thailand.

In conclusion, CaOx stone has the highest prevalence in every region of Thailand. Relatively high frequency of UA stone was documented. UA stone was likely to occur in the elderly whereas CaOx stone was likely to affect the middle-age peoples. The major dietary habits of kidney stone patients were inadequate water intake, high ingestion of polished rice as well as low intake of fruits and vegetables. We suggest that by changing dietary habits by drinking sufficiently fluids and eating more fruit and vegetables, as well as restricting purine-containing nutrients may help to reduce the stone forming potential and thereby reduce its morbidity.

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