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Urolithiasis in Udon Thani Hospital : A rising prevalence of uric acid stone

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Objective : *To investigate the composition of urinary tract stones and prospectively identify the risk of urinary stone in Udon Thani province.*

Methods : *63 patients who were affected with urinary tract stone and admitted at Udon Thani Hospital from March to May 2005 were recruited into the study. Stone specimens were collected by urologists after open-surgery. The mineral composition of the urinary stone was analyzed with Fourier transform infrared spectroscopy (FTIR). The patients were also interviewed directly regarding their general health and dietary habit.*

Results : *The mean age of the patients was 48.5 ± 13.1 years old. Male (33, 52.4 %) to female (30, 47.6%) ratio were 1.1:1. The difference between the prevalences of the new (54.0 %) and recurrent (46.0 %) cases was not statistically different. 34.9 % of the patients had relatives who had been affected with urolithiasis. Most patients consumed food of high-carbohydrate (90.5 %) and low-fat (66.7 %) content daily. Their low daily intake of the citrus fruits was also observed. Pure stones were accounted for 34.9 % (22/63) including calcium oxalate monohydrate (whewellite, 17.5 %), calcium oxalate dihydrate (weddellite, 3.2 %), magnesium ammonium phosphate (struvite, 3.2 %) and uric acid (11.1 %) stones.*

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Mixed stones (65.1 %, 41/63) were mainly found in the present study of which calcium oxalate mixed with calcium phosphate (90.2 %, 37/41) was the predominant type. Calcium oxalate stone was accounted for 79.3 % according to the major mineral constituent. The peak age of patients with calcium oxalate stone was 41-50 years old, whereas 61-70 years old was in the cases of uric acid stone. The distribution of stone types was similar in male and female patients.

Conclusion : *Calcium oxalate was the most common type of stone which resembled the distribution of urinary tract stone worldwide. A relatively high prevalence of uric acid stone suggests an increased consumption of high-protein and purine-containing food among the inhabitants. However, high-carbohydrate and low-fat diet consumptions combined with low citrus fruit intake are chief dietary risks of stone development in the population.*

Keywords : *Urolithiasis, Stone composition, Calcium oxalate, Uric acid, Stone risk factor.*

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วัตถุประสงค์ : *การศึกษานี้มีวัตถุประสงค์เพื่อหาความชุกของนิ่วแต่ละชนิด และศึกษาปัจจัยเสี่ยงที่สัมพันธ์กับชนิดของก้อนนิ่ว*

วิธีการ : *เก็บตัวอย่างก้อนนิ่วภายหลังการผ่าตัดจากกลุ่มตัวอย่างผู้ป่วยโรคนิ่วที่เข้ารับการรักษา โดยการผ่าตัดที่โรงพยาบาลอุดรธานีระหว่างเดือนมีนาคมถึงพฤษภาคม 2548 จำนวน 63 ราย วิเคราะห์องค์ประกอบแร่ธาตุของก้อนนิ่วโดยวิธี Fourier transform infrared spectroscopy (FTIR) การเก็บข้อมูลของผู้ป่วยและปัจจัยเสี่ยงของการเกิดนิ่วโดยใช้แบบสอบถามและการสัมภาษณ์*

ผลการศึกษา : *อายุเฉลี่ยของผู้ป่วย 48 $\pm$ 13.1 ปี สัดส่วนของผู้ป่วยโรคนิ่วชาย (52.4 %) ต่อหญิง (47.6 %) เป็น 1.1:1 และสัดส่วนของผู้ป่วยใหม่ (54.0 %) และผู้ป่วยเป็นนิ่วซ้ำ (46.0 %) ไม่แตกต่างกันอย่างมีนัยสำคัญ พบผู้ป่วยที่มีประวัติการเป็นโรคนิ่วในหมู่เครือญาติร้อยละ 34.9 ผู้ป่วยส่วนใหญ่นิยมบริโภคอาหารที่มีคาร์โบไฮเดรตสูง (90.5 %) และไขมันต่ำ (66.7 %) และการรับประทานผลไม้ที่มีซิเตรทอยู่ในระดับต่ำ ผลการวิเคราะห์ชนิดของก้อนนิ่วพบนิ่วเชิงเดี่ยวร้อยละ 34.9 ประกอบด้วยนิ่วแคลเซียมออกซาเลตโมโนไฮเดรต (17.5 %) นิ่วแคลเซียมออกซาเลตไดไฮเดรต (3.2 %) นิ่วแมกนีเซียมแอมโมเนียมฟอสเฟต (3.2 %) และนิ่วกรดยูริก (11.1 %) นิ่วส่วนใหญ่เป็นนิ่วผสม (65.1 %) โดยนิ่วแคลเซียมออกซาเลตผสมกับแคลเซียมฟอสเฟตพบได้มากที่สุด (90.2 %) คือเมื่อแบ่งชนิดตามองค์ประกอบหลักพบว่าเป็นนิ่วแคลเซียมออกซาเลตมากถึงร้อยละ 79.3 ช่วงอายุเสี่ยงของนิ่วแคลเซียมออกซาเลตและนิ่วกรดยูริกคือ 41-50 ปี และ 61-70 ปี ตามลำดับ รูปแบบของการกระจายของนิ่วแต่ละชนิดในเพศชายและเพศหญิงไม่มีความแตกต่างกันอย่างมีนัยสำคัญ*

สรุป : *นิ่วแคลเซียมออกซาเลตมีความชุกสูงสุด ซึ่งเหมือนกับการกระจายของนิ่วทั่วโลก นิ่วกรดยูริกมีแนวโน้มพบสูงขึ้น ซึ่งบ่งชี้ว่าประชากรมีการบริโภคอาหารที่มีโปรตีนและพิวรีนสูงเพิ่มมากขึ้น อย่างไรก็ตามวัฒนธรรมการบริโภคอาหารที่มีคาร์โบไฮเดรตสูงและไขมันต่ำ รวมทั้งการไม่นิยมรับประทานผลไม้ที่มีซิเตรทยังเป็นปัจจัยเสี่ยงทางอาหารสำคัญของการเกิดนิ่วในภูมิภาคนี้*

คำสำคัญ : *โรคนิ่ว, องค์ประกอบของก้อนนิ่ว, นิ่วแคลเซียมออกซาเลต, นิ่วกรดยูริก, ปัจจัยเสี่ยงของนิ่ว*

Urolithiasis or urinary tract stone affects people worldwide with the prevalence ranging from 1 – 20 %. [1] The highest prevalence of urolithiasis (20 %) was reported from Saudi Arabia whereas the probability of stone occurrence in Europe and US was between 8 – 15 %. In Thailand, the highest prevalence was documented in the northeastern region with probability of 16.9 %.[2] Recurrent rate of urolithiasis is high, which is a significant problem in its therapy and management. After extracorporeal shock wave lithotripsy (SWL), over 50 % of stone patients had stone relapse in five years. [3] Recurrence of renal stone increases the probability of kidney dysfunction, which can cause a complication of renal failure in patients with multiple recurrent stones.

An imbalance of stone modulators (promoters and inhibitors) in urine causes the development of stones. Elevation of stone promoters (e.g., calcium, oxalate, phosphate and uric acid) or reduction of inhibitors (e.g., citrate, potassium, magnesium and anion biomolecules) creates supersaturated urine; consequently, nucleate crystals and agglomerate, and eventually calculi are formed.[4] Metabolic abnormalities causing an inequity of promoters and inhibitors such as hypercalciuria, hyperoxaluria, hyperuricosuria and hypocitraturia has been considered as metabolic risk. Hypocitraturia is a common disorder occurring in less than 50 % of the patients with nephrolithiasis. [5] Our study found that more than 80 % of stone patients resided in northeasten Thailand presented hypocitraturia phenotype; hypokaliuria and hyperoxaluria were also frequently accounted for.[6, 7] Hypocitraturic patients also have a higher risk of recurrent stone development.[8] Therefore, post-therapeutic management of stone patients is aimed to increase the excretion of urinary citrate in order to prevent the relapse of stone.[9] Supplement of alkali citrate salts and adequate consumption of citrus fruits have been suggested for the patients. [10-12]

A number of epidemiological and experimental studies have identified risk factors of stone occurrence which were classified into extrinsic and intrinsic factors. Intrinsic risk factors include, namely, genetic background, sex, age, body mass index and ethnic; whereas extrinsic risk factors were dietary habit, water consumption, life style, climate, occupation, drug and stress.[13, 14] Urolithiasis affects the male rather than the female; and, obese persons have a higher risk than the lean ones.[15, 16] Dietary factor is also a common risk of urolithiasis.Consumption of high-oxalate content and low-citrate food are associated with the propensity of stone formation. [17, 18]

According to the mineral composition, stones can be easily categorized into two main groups: calcium and non-calcium stones. Calcium stone is the most frequently found worldwide (80 %); it can be subdivided into calcium oxalate, calcium phosphate, and mixed calcium oxalate and calcium phosphate. Furthermore, calcium oxalate stone can be subcategorized into: calcium oxalate monohydrate (COM, whewellite), calcium oxalate dihydrate (COD, weddellite) and calcium oxalate trihydrate (COT) which is the least frequently found. Non-calcium stones have been found approximately 20 %, i.e., uric acid, magnesium ammonium phosphate or struvite, and cystein stones. There have been three methods employed for the analysis of stone composition: conventional wet chemical reaction, x-ray diffraction spectroscopy and Fourier transform

infrared spectroscopy (FTIR). FTIR method has been frequently used in stone research providing reliable and reproducible data hence it was employed in the present study. [19] This study was aimed to identify the type of urinary tract stone and assess the risk factors in urolithiasis patients in Udon Thani Hospital.

Materials and Methods

The current research was observational and prospective study. A total of 63 subjects recruited into the study were patients with urinary tract stone who were admitted at Udon Thani Hospital, Udon Thani province from March 2005 and May 2005 (3 months duration). Informed consent was required for all participants and the research protocol was approved by Ethics Committee, Faculty of Medicine, Chulalongkorn University.

Stone specimens were obtained by open-surgery, washed to remove debris, dried, ground into powder and kept at -20°C until analyzed. The stone powder was analyzed for mineral composition by FTIR technique. A questionnaire was used as a tool for raw data collection using direct interview method. The interview was performed after the patients have been completely recovered from the operation to ensure that they had well consciousness.

Two-sample test of proportion and two-sample t-test were performed, respectively, to assess the difference of the proportion and mean between two independent groups. $P < 0.05$ was considered as statistical significance. All descriptive and inference statistics were analyzed by Stata version 8 (Collage Station, TX)

Results

Characteristics of patients

In total, 63 urolithiasis patients underwent open-surgery participated in the study. Most patients (82.5 %, 52/63) lived in Udon Thani province from birth, whereas 17.5 % of patients were from the vicinity areas including Sakon Nakhon (3/63), Roi Et (3/63), Nong Khai (1/63), Nong Bua Lum Phu (1/63), Yasothon (1/63), Khon Kaen (1/63) and Nakhon Ratchasima (1/63). The male were 52.4 % (33/63), and the female 47.6 % (30/63) (Table 1). The male-to-female ratio was 1.1:1 and the proportion of male versus female were not significantly different ($P = 0.704$). The mean age of patients was 48.5 $\pm$ 13.1 years. Age comparison between the male (48.2 $\pm$ 10.5 years) and female subjects (48.9 $\pm$ 15.7 years) also shows no statistical difference ($P = 0.846$). The peak age of participants was between 31-60 years old (74.6 %, 47/63). However, four subjects (6.2 %) were younger than thirty years old were identified; they were all female. The education level of the patients was mostly primary school: 87.3 % were educated at primary school or lower (Some, however, did not receive any education). Their occupations included farming and laboring (79.4 %; 50/63), housewife (14.3 %; 9/63) and other minority (6.3 %, 4/63).

Analysis of stone composition

FTIR method was employed to analyze the type of urinary stones. The study found six types of mineral constituents including calcium oxalate monohydrate (COM), calcium oxalate dihydrate (COD), calcium phosphate (CaP), magnesium ammonium phosphate (MAP) or struvite, calcium carbonate (CaC), and uric acid (UA). The morphology and size of each stone type are shown in Fig. 1.

Table 2 shows frequency and percentage of each type of urinary stones reported in the study. The mixed-type of stone was accounted for 65.1 % (41/63), whereas the pure type of stone was found

34.9 % (22/63). Various types of mixed urinary stone were identified, i.e., calcium oxalate (CaOx) mixed with CaP (37/41); CaP mixed with CaC (2/41); CaP mixed with CaOx and CaC (1/41); and MAP mixed with CaOx and CaP (1/41). Pure stones were classified into, namely: COM (11/22), COD (2/22), MAP (2/22) and uric acid (7/22). CaOx (79.3 %, 50/63) was the most frequently stone found in the study population; seven out of 63 (11.1 %) were uric acid stone, ranking second.

Regarding the distribution of stones according to the age of the patient, it was found that the highest probability of CaOx stone was between 31 – 60 years old, whereas the peak age of uric acid stone was between 61 – 70 years old (Fig. 2). The distributions of urinary stone in the male and female patients were similar (Fig. 3).

Table 1. General data of patients.

Characteristics	**Frequency (%) n = 63**
Gender*	
Male	33 (52.4)
Female	30 (47.6)
Age (years)	
< 20	1 (1.6)
21-30	3 (4.8)
31-40	12 (19.0)
41-50	20 (31.7)
51-60	15 (23.8)
61-70	8 (12.7)
> 70	4 (6.3)
Education level	
Primary school and lower	55 (87.3)
Secondary school	7 (11.1)
Higher than secondary school	1 (1.6)
Occupation	
Farmer and labor	50 (79.4)
Housewife	9 (14.3)
Local government officer	2 (3.2)
Others (student, monk)	2 (3.2)
Recurrence of stone*	
First episode (new case)	33 (54.0)
Recurrent episode (recurrent case)	29 (46.0)

* two-samples test of proportion, P > 0.05

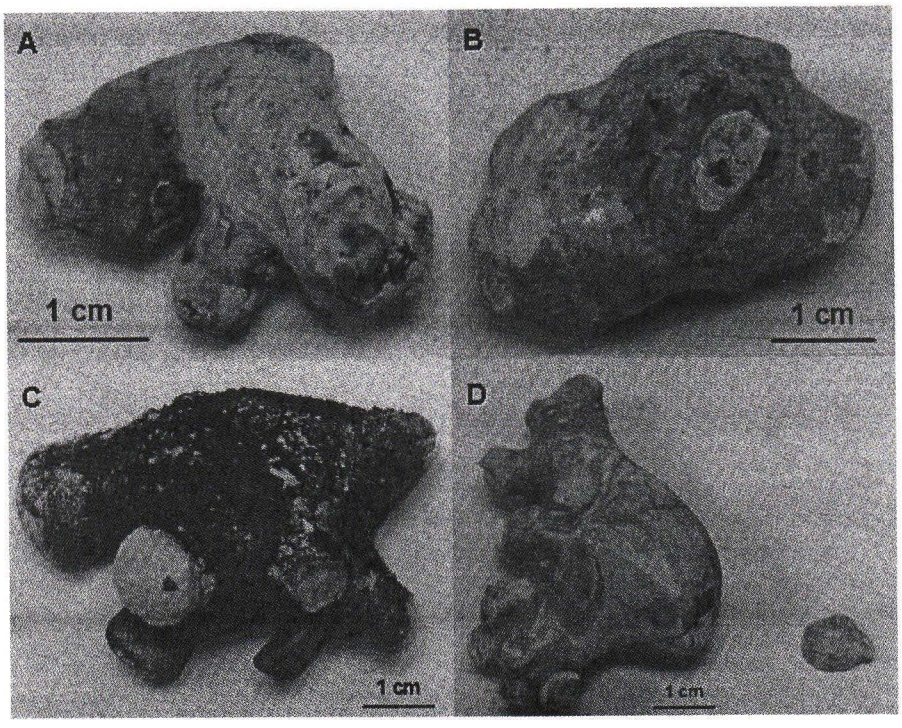

Figure 1. Morphology of urinary stones: A, calcium oxalate monohydrate stone; B, magnesium ammonium phosphate stone; C, calcium oxalate mixed with calcium phosphate stone; D, uric acid stone.

Table 2. Frequency of each stone type.

Type of stones	Frequency (%)
Number of cases	63 (100.0)
Pure stone	22 (34.9)
COM	11 (17.5)
COD	2 (3.2)
MAP	2 (3.2)
UA	7 (11.1)
Mixed stone	41 (65.1)
COM + CaP	31 (49.2)
COD + CaP	6 (9.5)
CaP + CaC	2 (3.2)
CaP + COM + CaC	1 (1.6)
MAP + COM + CaP	1 (1.6)
Stone types regarding to major component	
CaOx	50 (79.3)
UA	7 (11.1)
CaP	3 (4.8)
MAP	3 (4.8)

Abbreviation: COM; calcium oxalate monohydrate, COD; calcium oxalate dihydrate, CaP; calcium phosphate, MAP; magnesium ammonium phosphate (struvite), CaC; calcium carbonate, CaOx; calcium oxalate, and UA; uric acid

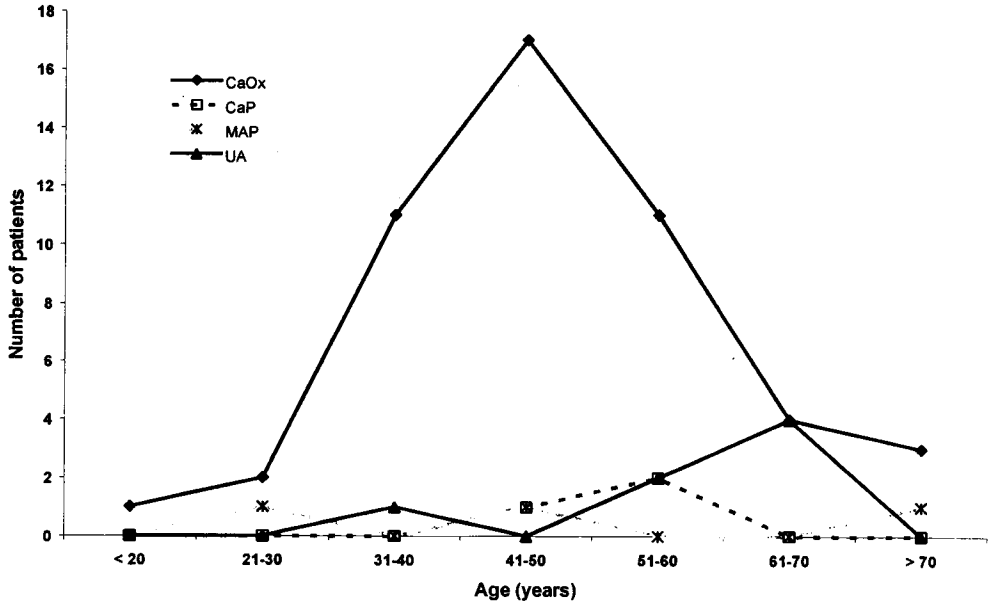

Figure 2. Age distribution of each stone type: CaOx, calcium oxalate stone; CaP, calcium phosphate stone; MAP, magnesium ammonium phosphate stone (struvite); UA, uric acid stone.

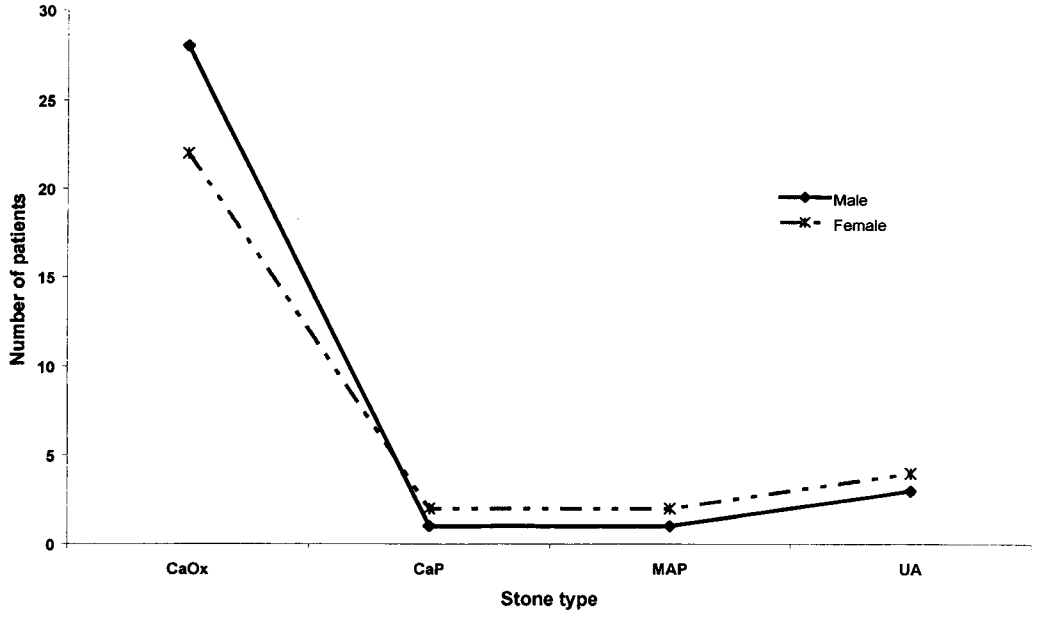

Figure 3. Distribution of stone types compared between the male and female patients. CaOx: calcium oxalate stone; CaP: calcium phosphate stone; MAP: magnesium ammonium phosphate stone (struvite); UA: uric acid stone.

Risk factors of urinary stone

Urinary stone of first episode was found in 54 % of the patients while the rest 46 % were patients were recurrent. The proportions of the new and recurrent cases of urinary stone were not significantly different (P = 0.527) (Table 1). The proportion of the patients who had no history of relatives affected with urinary tract stone (65 %) was significantly higher than those who had the history (35 %) (P = 0.023) (Fig. 4).

Assessment of dietary risk factors found that the proportion of patients who had water intake >2 liter/day (54 %) was higher than those who intake water <2 liter/day (46 %) but it was not of statistical significance (P = 0.527) (Fig. 4). Over 90 % of the patients consumed sticky rice daily (high-carbohydrate content food). Moreover, 66.7 % of the patients preferred to consume food with low-fat content daily. Intake of the citrate fruits in the study population was very low (Fig. 5). The patients preferred local vegetables which contain high-oxalate content such as *Amaranth* (*Khom*), *Variegatum* (*Cha Plu*), *Gratoxylum formosum (Teuw)*, *Careya Sphaerica* (*Kra Done*), and *Acacia Pennata* (*Cha Om*). Also, the intake of milk with high-calcium content was very low.

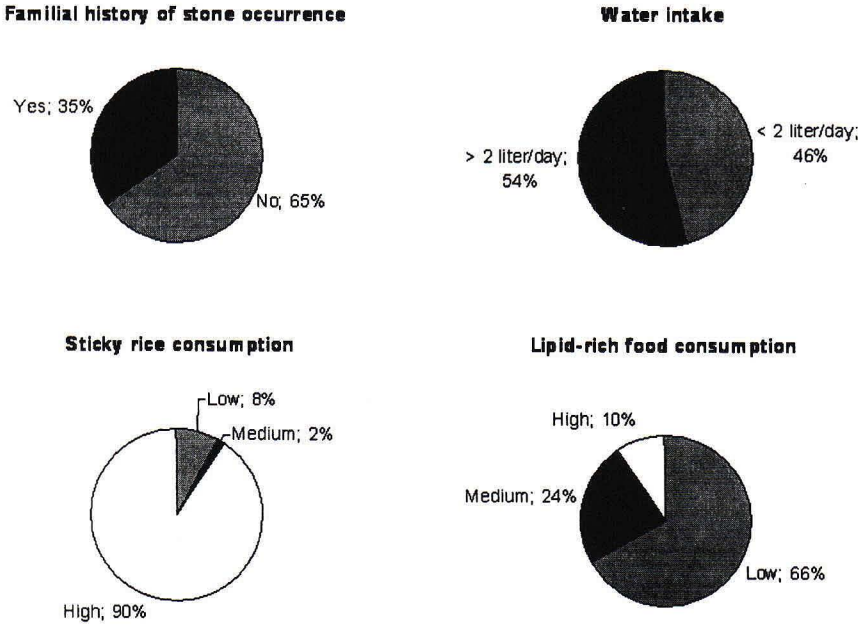

Figure 4. Assessment of urolithiasis risk factors including familial history of urinary stone, dietary factors, water intake, high-carbohydrate food (sticky rice) consumption and low-fat diet intake.

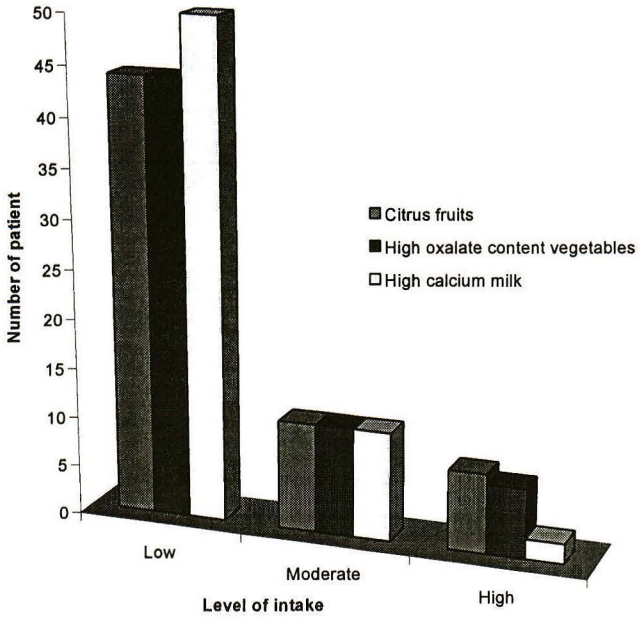

Figure 5. Estimation of levels of intake of fruit of high-citrate content (citrus fruits), vegetable of high-oxalate content, and milk of high-calcium content in patients with urinary tract stone.

Discussion

The prevalence of stone types and risk factors were investigated in the present study. The proportion of the male and female patients affected with urolithiasis seems to be similar in the study. Various studies reported that the male had 2-3 folds of probability higher of stone incidence than the female. The effect of estrogen in female can increase excretion of citrate (potent stone inhibitor) in urine. [15] On the other hand, testosterone in male enhances the synthesis of oxalate (critical stone promoter) in the liver. Thus men have higher oxalate and lower citrate concentrations in urine than women, providing a higher stone forming propensity. Possibly, an increasing proportion of the female patients in the present study suggests that extrinsic risk factors such as dietary factor and change of life style may involve formation of urinary stone. Age of risk of urinary stone between 31-60 years old is consistent with other reports.[20]

The occupations of the study population, particularly farmers and labors, were prone to urinary stone formation. Extensive work in the field in combination with the hot weather which increase sweat loss and decrease urine volume, they directly cause the depletion of potassium electrolyte and create supersaturated urine. Moreover, a long-term potassium depletion leads to intracellular acidosis of the renal cells which consequently increases the reabsorption of citrate resulting hypocitraturia. [5, 21] In addition, exposure to the ultraviolet induces the production of vitamin D which in turn increases the intestinal absorption of calcium and eventually causes the increment of excretory calcium in urine.

Familial risk has been reported in about 16 – 37 % of urinary stone patients who had relatives who had experienced urolithiasis.[13] Our data also show a

consistent figure with positive familial history of 35 %. This again suggests the influence of external risk over the internal one. Further, it should be noted that occurrence of urinary stone among relatives may be due to living in the same environment and also having similar dietary habits, life styles and activities.

So far, dietary factor is an important risk of urinary stone occurrence. Inaporopriate intake of food could be propensity of urinary stone formation, i.e., high-protein diet causes high excretion of calcium and uric acid in urine.[22] Our previous data collected form northeastern patients with urinary stone found that most patients daily consumed high-carbohydrate and low-fat food combined with low intake of citric acid-rich fruits led to hypocitraturia.[7,23] Reabsorbed citrate is catabolized by ATP citrate lyase yielding oxaloacetate and acetyl CoA. The latter product enters the fatty acid biosynthesis pathway in order to compensate the low dietary lipid intake. Similar pattern of dietary habit was observed in this study, emphasizing the cultural conservation. In addition, the patients preferred to ingest local vegetables rich in oxalate contents. Although the level of the intake is relatively low, but when it is regularly consumed this may cause an elevation of urinary oxalate concentration contributing the stone forming tendency. Hence, increased consumption of lipid-containing food as well as citrus fruits were recommended for these patients in order to reduce the risk of stone relapsing.

The present data show that calcium oxalate stone was the most frequently found urinary stone (Table 2), similar to the worldwide reports of stone distributions. In Europe, calcium oxalate stone was documented 61 %, [20,24] and the greater prevalence was found in Japan (82 %) [25] and India (93 %).[26] Recently, calcium oxalate stone of 66 % was reported in southern Thailand. [27] Most studies, however, found that pure stones were more prevalent than the mixed ones, but this is opposite to that found in our study. Our data revealed that calcium oxalate mixed with calcium phosphate was the most common stone. The contradiction suggests that the mechanism of stone formation may be different from region to region. Hyperoxaluria with hyperphosphaturia may be the main metabolic risks in our patients. Basically, CaP crystals are formed in earlier sections 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 can nucleate CaOx in later nephron segments in metastable urine; thus, heterogeneous nidus (stone core) is predominantly initiated. [28]

A relatively high prevalence of uric acid stone was found in our study. People aged 61-70 years were at risk of uric acid stone which was older than the age of risk calcium oxalate stone (41-50 years). Uric acid stone was caused from hyperuricosuria and contributed by low urinary pH (pH < 5.5). High intake of high-protein and purine-containing diets directly cause hyperuricosuria.[29] Additional source of purine is alcohol beverages, particularly beer. The finding of high prevalent uric acid stone may suggest a diversity of dietary pattern in the study region. However, other causes of hyperuricosuria and acidic urine pH, such as genetic defect and underlying diseases, cannot be ruled out. Further investigation to identify the actual cause of high uric acid stone incidence remains to be conducted.

Some limitations of the study should also be noted, i.e., patients who underwent lithotripsy were left out of the data since the collected stone specimens were obtained only from open-surgery. The difficulty of collection of small stone fragments excreted after lithotripsy was the cause. The study was conducted only at the Udon Thani Hospital therefore the results may be too limited to be generalized. Nevertheless, the fact that the study population mostly inhabited in the Udon Thani province could allow them to be good representatives for urolithiasis population in the province.

In conclusion, calcium oxalate stone has the highest prevalence of urinary stone in Udon Thani. Relatively high frequency of uric acid stone was also documented. Change of stone distribution implies a change of dietary habit and life style in among the inhabitants. Uric acid stone was likely to occur in the elderly whereas calcium oxalate stone was likely to affect the middle-age group. The main dietary risk was high-carbohydrate, low-fat food ingestion as well as low intake of citric acid-rich fruits. This suggests that changing dietary habit to consume more citrus fruits (e.g., orange, tangerine, lemon, lime, grapefruit and pineapple), restrict purine-containing diets (e.g., alcoholic beverages, organ meat, sardines, asparagus and kidney bean) and intake sufficiently lipid-containing foods (e.g., stir fry recipes, fried noodle and curries) may provide a beneficial effect on urinary stone prevention, particularly in inhabitants with age over 40. Thus, moderation of balanced dietary habit combined with health promotion programs should be encouraged to reduce the incidence of urolithiasis among this population. [30, 31] Further investigation of the definite cause of high prevalent uric acid stone still remains a challenge.

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