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ORIGINAL PAPER

Metabolic disturbances in Chinese children with urolithiasis: a single center report

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Abstract Urinary stones and urine composition are the first steps in the process of recurrence prevention, but data concerning the association between the two compositions are scarce in Chinese children with urolithiasis. We retrospectively analyzed the records of children (age range 0–18 years) with urolithiasis in our center between March 2004 and December 2013. Stone analysis was carried out in 382 children and 24-hour urine analysis in 80 children. Analysis of both stone and 24-hour urine composition was completed in 56 children. Stone samples were analyzed by Fourier transform-infrared spectrometry. The major stone constituents were calcium oxalate (78.8 %). Of 80 children with 24 h urine analysis, only 2.5 % were without urinary metabolic abnormalities. Hypocitraturia was recorded in 97.5 %, high sodium excretion in 50.0 %, cystinuria in 48.7 %, hypercalciuria in 18.8 %, small urine volumes in 12.5 %, hyperoxaluria in 5.0 % and hyperuricosuria in 1.3 %. Interestingly, higher urine volumes were recorded in girls than in boys (73.2 ± 58.5 vs 51.3 ± 45.3 mL/kg, $p = 0.036$). Urine sodium ($p = 0.002$) and oxalate ($p = 0.004$) were significantly higher in children >9 year old. Moreover, compared with calcium oxalate stone formers, the urine volume ($p = 0.040$), citrate ($p = 0.007$) and cystine ($p = 0.004$) were higher in patients with cystine stones. Hypocitraturia was the common abnormality among Chinese children with urolithiasis. The surprisingly high incidence of cystinuria is of note.

Keywords Pediatry · Metabolism · 24-h urine analysis · Urolithiasis

Introduction

Pediatric urolithiasis is a relatively rare disease with prevalence between 2 and 2.7 % [1]. However, in recent years, increasing incidence has been reported in different studies [2, 3]. Moreover, high recurrence rates usually requiring multiple surgical interventions also occur in children with urolithiasis. This problem is associated with high management costs and potential risks for end-stage renal disease [4].

In comparison with healthy children, those with stone disease are more likely to have urinary metabolic abnormalities [1, 3]. Moreover, many children with stones have anatomical malformations. Despite active removal of existing stones, further stone formation is not prevented. The patients therefore should be thoroughly evaluated and educated on how to counteract new stone formation. An elaborate metabolic evaluation is helpful for understanding the causes of stone formation in the individual child and in accordance with the findings; an appropriate recurrence preventive regime should be designed. Knowledge of 24-h urine and stone composition are fundamental prerequisites for selecting the most appropriate method aiming at prevention of kidney stone recurrences [5]. Nevertheless, data that provide accurate information on 24-h urine and stone composition in children are scarcely reported in China.

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The objective of this study was to analyze and summarize the characteristics of 24-h urine and stone composition in a population of Chinese children with urolithiasis.

Materials and methods

Ethics statement for collection of stone and urine samples

This study was approved by the Ethics Review Board of Guangzhou Medical University, Guangzhou, China. Ethics Review Board specifically approved that not informed consent was required because data were going to be analysed anonymously. Stone and urine samples were obtained from patients, which were collected following the first affiliated Hospital of Guangzhou medical University.

Subjects

Between March 2004 and December 2013, the records of children (age range 0–18 years; in- and out-patients) with urolithiasis diagnosed by ultrasound, KUB or CT scan in our center were retrospectively reviewed. Stone analysis was carried out in 382 children. 24- urine analysis was carried out in 80 children who can collect a complete 24-h urine by themselves or with the help of their parents. The collection process was under professional's supervision to ensure the integrity of 24-h urine. Both stone and urine analysis were completed in 56 children.

Methods

All stone samples were analyzed by Fourier Transform-Infrared spectrometry (Thermo, USA). Stones were classified according to their main stone component. The only exception was stones containing cystine which were classified as cystine stones irrespective of the cystine fraction. Stones composed of magnesium ammonium phosphate, carbonate apatite and/or ammonium urate were classified as infection stones.

Urine produced during 24 h was collected from 80 patients before stone removal. All patients were on their habitual and self-selected diet. Urine biochemical variables including urine volume, calcium, magnesium, sodium, urate, phosphate, cystine, oxalate and citrate were measured. Urine oxalate and citrate were measured by ion exchange chromatography (Metrohm, Switzerland). Urine calcium, magnesium, sodium, phosphate and urate were assessed by an automatic biochemical analyzer (Beckman-Coulter, America). Urine cystine was measured by Multiskan Ascent (Thermo, USA).

Statistical analysis was made with SPSS statistical software version 13.0. All continuous variables were expressed as mean ± SD. Chi-square test was used to compare group frequencies and gender differences. Independent-sample *t*-test and Mann–Whitney U test were used for group comparison. A p value of less than 0.05 was considered statistically significant.

Reference standard

Standard laboratory 24-h normal urine values for children were used according to those published in the literature [6, 7] with the following definitions: hypocitraturia <365 mg (1.90 mmol) of citrate/1.73 m^2/days for boys and <310 mg (1.61 mmol)/1.73 m^2/days for girls; hypercalciuria >4 mg (0.10 mmol)/kg/days of calcium; hyperoxaluria >40 mg (0.44 mmol) of oxalate/1.73 m^2/days; hyperuricosuria >815 mg (4.85 mmol) of urate/1.73 m^2/days; high sodium excretion >69 mg (3.0 mmol)/kg/days for both genders; cystinuria >75 mg (0.31 mmol)/1.73 m^2/days of cystine. Small 24-h urine volume was defined as <20 ml/kg/days.

In addition, the ion-activity product of cystine ($AP_{CYSTINE}$) was calculated according to the formula below in which the cystine concentration ($C_{CYSTINE}$) is expressed in moles per liter [23]. The formation (FP) and solubility products (SP) of cystine are approximately 1.3×10^{-20} and 1.0×10^{-20} $(mol/L)^3$, respectively.

$$AP_{CYSTINE} = \frac{(10^{-pH})^2 \times C_{CYSTINE} \times 0.155}{\left[1 + (0.39 \times 10^9 \times 10^{-pH}) + ((10^{-pH})^2 \times 3.51 \times 10^{16})\right]}.$$

Results

Stone constituents in the 382 analyzed stones were as follows: 301 (78.8 %) calcium oxalate, 41 (10.7 %) infection stone 36 (9.4 %) cystine and 4 (1.1 %) uric acid. There was a male predominance of 247 boys (64.7 %) and 135 girls (35.3 %), with the ration was 1.8:1.

According to literature reference values [6, 7], only 2 (2.5 %) of the 80 samples of 24 h urine were without abnormalities. The most commonly encountered risk factor was low citrate in 97.5 % of the patients; Excessive sodium excretion was recorded in 50.0 %, cystinuria in 48.7 %, hypercalciuria in 18.8 %, small urine volumes in 12.5 %, hyperoxaluria in 5.0 %, and hyperuricosuria in 1.3 % of the patients. Moreover, 12 % of these patients had $AP_{CYSTINE}$ above $FP_{CYSTINE}$ and another 9 % had $AP_{CYSTINE}$ values above $SP_{CYSTINE}$.

There were no statistically significant differences in frequencies of urinary abnormalities between boys and girls. The results are shown in Table 1. Abnormal urine composition also had male predominance with 46 boys (57.5 %)

Table 1 Frequency (%) of urinary abnormalities in pediatric stone patients

	All children	Boys	Girls	*p* value*
Small urine volume	12.5	17	6.1	>0.05
Hypercalciuria	18.8	23.4	12.1	>0.05
Hypocitraturia	97.5	100	93.9	>0.05
Hyperuricuria	1.3	2.1	0	>0.05
Hyperoxaluria	5	2.1	9.1	>0.05
Hypomagnesemia	11.3	14.9	6.1	>0.05
High urine sodium	50	57.4	39.4	>0.05
Cystinuria	48.7	48.9	48.5	>0.05

* $p < 0.05$ was considered statistically significant

and 32 girls (40.0 %). A comparison between the genders disclosed that the urine volumes were larger in girls than in boys: 73.2 ± 58.5 vs 51.3 ± 45.3 mL/kg, respectively, $p = 0.036$. All other urine variables did not differ significantly between boys and girls ($p > 0.05$).According to age groups, urine sodium ($p = 0.002$) and oxalate ($p = 0.004$) were significantly higher in children >9 years old. The urinary findings are summarized in Table 2.

In the 56 children with both stone and 24-h urine analysis, 27 (48.2 %) had calcium oxalate stones, 20 (35.7 %) cystine stones, 8 (14.3 %) infection stones whereas only one child (1.8 %) had uric acid stone. When the 24-h urine composition was compared between calcium oxalate and cystine stone formers, results showed that the 24-h urine volumes ($p = 0.040$), as well as the excretion of citrate ($p = 0.007$) and cystine ($p = 0.004$) were significantly higher in patients with cystine stones (Table 2).

In Table 3, the recorded abnormalities are stratified according to stone composition in children with calcium oxalate, cystine, infection and uric acid stones. The incidence of hypocitraturiain the four types of stone composition was similarly high, not significantly different. But cystinuria was also found in calcium oxalate and infection stone patients (37.3, 25 %, respectively) although the rate is significantly lower than cystine stone patients (70 %).

Table 3 Percentage of urinary abnormalities in children stratified according to stone composition

	Calcium oxalate	Cystine	Infection	Uric acid
No. children	27	20	8	1
Low urine volume	22.20 %	0	25 %	0
Hypercalciuria	14.80 %	10 %	0	0
Hypocitraturia	100 %	90 %	100 %	100 %
Hyperuricuria	0	5 %	0	0
Hyperoxalaturia	0	10 %	0	0
Cystinuria	37.30 %	70 %	25 %	0

Discussion

Although urinary stone composition and 24 h urine composition analysis are very important in the process of stone recurrence prevention, only few studies have focused exclusively on the pediatric population. Information in this regard is also meager in other populations in the world. So far, no data have been published on the 24-h urinary abnormalities in Chinese children. The intention of our study was to review data from our center with the aim of drawing conclusions on discriminating features that might serve as a reference for design of recurrence preventive regimens.

Table 2 Demographics and urine constituents in different age, boys and girls, and in calcium oxalate and cystine stone forming children patients

	Boys	Girls	Calcium oxalate	Cystine	0–9 years	9–18 years
Number children	47	33	27	20	52	28
Age	7.0 ± 4.3	5.6 ± 3.2	7.5 ± 4.1	6.2 ± 4.0	4.2 ± 2.3	11.0 ± 2.2
Urine urinary excretion of different variables (mean ± SD)						
Volume (mL/kg)	51.3 ± 45.3#	73.2 ± 58.5#	59.2 ± 62.9*	69.4 ± 37.4*	54.9 ± 46.9	70.3 ± 60.8
Calcium (mmol/kg)	0.069 ± 0.059	0.053 ± 0.080	0.053 ± 0.040	0.058 ± 0.036	0.069 ± 0.079	0.077 ± 0.059
Magnesium (mmol/kg)	0.083 ± 0.055	0.108 ± 0.117	0.075 ± 0.051	0.063 ± 0.029	0.098 ± 0.099	0.083 ± 0.058
Sodium (mmol/kg)	3.9 ± 2.00	4.61 ± 3.39	3.86 ± 3.02	4.07 ± 2.02	3.32 ± 2.23&	5.24 ± 3.25&
Oxalate (mmol/kg)	0.008 ± 0.007	0.013 ± 0.016	0.013 ± 0.016	0.009 ± 0.008	0.008 ± 0.007&	0.014 ± 0.016&
Citrate(mmol/kg)	0.031 ± 0.019	0.042 ± 0.046	0.025 ± 0.0169*	0.049 ± 0.038*	0.030 ± 0.027	0.044 ± 0.043
Urate (mmol/kg)	0.095 ± 0.076	0.103 ± 0.065	0.081 ± 0.050	0.094 ± 0.046	0.095 ± 0.077	0.102 ± 0.059
Cystine (mmol/kg)	0.068 ± 0.094	0.099 ± 0.162	0.054 ± 0.083*	0.151 ± 0.177*	0.092 ± 0.151	0.065 ± 0.077

# $p < 0.05$ the values differed significantly between the genders

* $p < 0.05$ the values differed significantly between calcium oxalate and cystine stone forming children

& $p < 0.05$ the values differed significantly between the age

As expected, we found that calcium oxalate was the predominant urinary stone constituent, encountered in 78.8 % of the children. This finding was in agreement with reports from Tunisia [8] and Armenia [9], but the occurrence of calcium oxalate stones was lower than that in Europe [10]. The incidence of stones composed of uric acid was clearly below that recorded in other reports [9, 10]. This observation might be a reflection of dietary habits or genetically explained differences compared with populations in other countries. Cystine stone formation, the result of a genetic disease, was observed in 0.4 % of males and 0.7 % of females in the largest published series of pediatric stone analyses in Europe [10]. In our study, however, cystine stone comprised nearly 10 % of all pediatric stones. Precipitation of cystine is the clinical manifestation of cystinuria which is monogenic disease. The reason for this pronounced discrepancy might be the more frequent occurrence of cystinuria in Chinese children with urolithiasis. In comparison with our previous research, there was a different distribution of stone species in children than in adults [11].

Urinary abnormalities were present in 97.5 % of our children according to reference values. Low citrate excretion was the major urinary risk factor in stone formation. It is of note that hypocitraturiain our study was much more common than results recorded in other analyses of 24-h urine samples [6, 12–14]. In available publications, the highest percentage (63 %) for hypocitraturia was reported in a study from Pakistan [12]. In most other reports hypocitraturia was in the range of 20–58 % [6, 13, 14].

Hypocitraturia has been shown to be a powerful risk factor for recurrent stone disease in children [7]. It is generally known that citrate is an inhibitor of the crystallization of calcium salts. Citrate decreases the concentration of ionized calcium and will accordingly favorably reduce the ion-activity products of both calcium oxalate and calcium phosphate. Citrate also has the ability to prevent nucleation, agglomeration and growth of calcium oxalate and calcium phosphate crystals in final urine as well as in renal tubular urine [15]. By protecting tubular cells from injury lipid per-oxidation will be counteracted [16]. These current findings all show that citrate is an important determinant in the calcium oxalate crystallization process. In view of these properties, it is of note that our examination of urine composition disclosed significantly lower citrate excretion in children who had formed calcium oxalate stones than in those who had formed cystine stones. Although the reasons for hypocitraturia is incompletely understood, risk factors include a high animal protein diet, medullary sponge kidney disease, metabolic acidosis in chronic diarrhea syndrome and lactic acidosis [17]. The systemic and intracellular acidosis secondary to complete and incomplete distal renal tubular acidosis also lead to decreased citrate excretion [6]. Genetic and ethnic factors might also play a role, because our previous study showed significant differences in citrate excretion between adult Chinese stone formers compared with that in adults from other countries [18]. For calcium stones patients with idiopathic hypocitraturia, pharmacological treatments that increase urinary citrate might be an effective method for preventing stone recurrences. In a randomized, placebo-controlled trial in calcium stones patients with idiopathic hypocitraturia, a significantly decreased stone recurrence rate was demonstrated in patients treated with potassium citrate compared with those who received placebo [19].

In pediatric urolithiasis, the incidence of cystine stone disease obvious is higher than in adults [11]. A recent report showed that children with cystine stones had an earlier start of stone formation than those who formed stones composed of calcium oxalate [20]. This is in line with our results. Different from the mechanisms behind calcium oxalate stone formation, the only etiology of cystine stone formation is the high urinary excretion and supersaturation with cystine. We found that the incidence of cystinuria and mean urinary cystine excretion was higher in our children than those recorded in previous studies from other countries [15, 21, 22]. The fraction of patients whose $AP_{CYSTINE}$ level was above $FP_{CYSTINE}$ was also high in our study. $FP_{CYSTINE}$ is the approximate level of $AP_{CYSTINE}$ at which nucleation is assumed to occur. It is the level of $AP_{CYSTINE}$ that is of clinical importance and the basis for recurrence preventive considerations [23]. The surprisingly high percentage of children with cystine stone formation, reflects the fact that cystinuria was a very common diagnosis in Chinese children. The explanation for the high frequency of increased cystine excretion might be that heterozygous genetic abnormalities with slightly increased urinary cystine are more common in this population. Cystinuria is a genetic defect in the transport of the amino acids cystine, arginine, lysine and ornithine, resulting in an impaired reabsorption in the renal proximal tubule and the small intestine [20]. Cystinuria is divided in type A, type B, and type AB. In type A, the disease is caused by mutations in alleles of the SLC3A1 gene in chromosome 2. In type B heterozygotes the mutation is located in the SLC7A9 gene on chromosome 19. Patients with the rare type AB cystinuria have two mutated alleles in both chromosomes [24].

The mainstay of recurrence prevention in cystine stone-forming patients is to decrease the urine concentration of cystine and thus reduce $AP_{CYSTINE}$ to levels belowing the risk of crystal nucleation. Increased urine flow and urine pH are the common conservative treatment measures. The 24-h urine usually needs to be increased to at least 3 L and the optimal urine concentration of cystine should be less than 250–300 mg/L (~1.05–1.25 mmol/L) [25]. Therefore, the high urine flow must be maintained also during the

night hours, but most patients find it difficult to cope with such a regimen. Alkalizing beverages such as mineral water and citrus juices are recommended to increase urine pH [26]. Pharmacologic therapy, with D-penicillamine (DP), alpha-MPG and tiopronin, produce cysteine complexes, which are 50 times more soluble than cystine [27, 28]. These drugs can effectively decrease urine concentrations of cystine during the day and night. The latter treatment is, however, not without side effects.

Formation of kidney stones with other constituents is also the result of high urine concentrations and supersaturation with the stone forming salt; mainly calcium oxalate and calcium phosphate. Increased fluid intake is a simple and cheap strategy to prevent urolithiasis. Previous results showed that increased fluid intake with urine production target of >2000 mL/day had preventive effects of calcium oxalate stone recurrence in adult patients [29]. We found that the 24-h urine volumes in boys were lower than those in girls with urolithiasis. The explanation for that is unclear, but this condition might have contributed to the higher incidence of urolithiasis in boys [10]. In addition to gender, urine sodium and oxalate were significantly higher in children >9 years old (Table 2). Excessive intake of salt and oxalic acid food are common in China. Although some studies emphasized that increased dietary sodium increases the risk of calcium stone formation [30, 31], Eisner et al. reported that urine sodium was associated with increased urine calcium and volume, and decreased urine calcium oxalate supersaturation (SSCaO*x*), which is a potential protective effect of sodium in these patients in regard to stone risk [32].

There are limitations in our findings inherent in the retrospective nature of this study. Retrospective series are restricted by the completeness of detail present in the medical records. We are unable to provide more detailed data on 24 h urine. In addition, children with anatomical abnormalities were ignored in our study, which may affect the results. Finally, it is of note that there is a lack of reference values for 24-h urine composition in Chinese children. We did not have the possibility to compare the data between stone forming and non-stone forming children. In order to get a more practical result, further epidemiological multicenter studies are desirable. It needs to be emphasized, however, that hypocitraturia seems to represent a very common abnormality among Chinese calcium oxalate stone forming children and that therapeutic efforts should have its focus on this pathology.

Urinary metabolic risk-factors for urolithiasis were identified in almost all children, with hypocitraturia being the most common only encountered abnormality. Our data suggest that low urine output and hypocitraturia were more for calcium oxalate than for cystine stone formation. The unexpected and exceptionally high incidence of cystinuria should be noted. Different treatment regimens should be designed according to the specific abnormalities.

Compliance with ethical standards

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Conflict of interest No competing financial interests exist.

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