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An association between kidney stone composition and urinary metabolic disturbances in children

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Abstract *Objective:* To determine kidney stone composition in children and to correlate stone fractions with urinary pH and metabolic urinary risk factors.
Patients and methods: We studied 135 pediatric patients with upper urinary tract lithiasis in whom excreted or extracted stones were available for analyses. Composition of stones was analyzed. A 24-hour urine assessment included volume, pH and daily excretions of calcium, oxalate, uric acid, cystine, creatinine, phosphate, magnesium and citrate.
Results: Calcium oxalate was the major component of 73% stones, followed by struvite (13%) and calcium phosphate (9%). Uric acid was present in almost half of stones, but in rudimentary amounts. The calcium oxalate content in calculi showed a strong relationship with calciuria, and moderate association with oxaluria, magnesuria and acidification of urine. The percent content of struvite presented reverse and lower correlations with regard to the above parameters. Calcium phosphate stone proportion had low associations with urinary risk factors.
Conclusions: Calciuria, oxaluria, magnesuria and low urine pH exerted the biggest influence on calcium oxalate content in pediatric renal stones. Relationships of urinary risk factors with calculi calcium phosphate content were of unclear significance. Urinary citrate excretion did not significantly correlate with kidney stone composition in children.

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Introduction

Evaluation of urinary stone composition is an important diagnostic step in determining the possible etiology and pathophysiologic mechanisms of stone formation. Effective crystal formation takes place when urine is supersaturated with stone-forming salts and, thus, the calculi composition should correspond with specific admixture's urine saturation [1,2].

In cases of struvite ($MgNH_4P$) and cystine stones, these associations with chronic infection of the urinary tract with urea-splitting organisms and cystinuria, respectively, are clearly shown. However, for most common calcium stones, the presence of several risk factors, including hypercalciuria, hyperoxaluria, hypocitraturia and hyperuricosuria was reported [3,4]. Moreover, the composition of most of the calculi is not homogeneous. In developed countries, calcium oxalate (CaOx) is the predominant stone constituent usually admixed with small amounts of calcium phosphate (CaP) and/or uric acid (UA), which may form the initial nidus of the CaOx stone. Only in a limited number of cases do substances different from CaOx constitute the main stone phase [5,6].

In children, the reported compositions of stones slightly differ from those in adults. They are often made of a larger number of constituents reflecting a specific complex structure. Another important feature of pediatric urinary stone disease is the prevalent proportion of cases with coincident metabolic disturbances in urine. Excretion rates of calcium, oxalate, citrate and uric acid are higher when adjusted for urine creatinine. Calcium oxalate supersaturation is similar to that in adults, but calcium phosphate supersaturation is usually higher whereas uric acid is lower because of higher urine pH at pediatric age [7–12].

In fact, only few reports to date have focused on the association between different stone components and biochemical urinary risk factors in children [10,11]. Therefore, the purpose of this study was to define the correlations between stone constituents and urinary pH, and accompanying metabolic abnormalities in urine in pediatric kidney stone formers.

Patients and methods

Study population

This retrospective study was carried out using the data of 135 patients with upper urinary tract lithiasis (71 boys, 64 girls), aged 2–18 years (median 14.6 years), treated in the University Children's Hospital in Bialystok, Poland during 2002–2011. There were two main inclusion criteria for the study: availability of the stone for chemical analysis and appropriate 24-hour urine collection. There were no other exclusion criteria if complete urinary metabolic and stone composition results were attainable. The study included 36% of urolithiasis patients registered in the hospital records during that period. In the remaining children, stones were not excreted or were unavailable because of loss/unnoticed spontaneous passage.

Calculi were obtained intact from spontaneous passage (81), open surgery (26) or fragmented form after ureterorenoscopic lithotripsy (15), extracorporeal shock wave lithotripsy (12) or percutaneous nephrolithotripsy (1). In 26 traditionally operated children, 10 had staghorn calculi and concomitant pyeloureteral junction obstruction was suspected in 11. Twenty-one patients submitted more than one stone during that time, but only primary stone analyses and urinary chemical profiles were considered in the study. Thirteen stone formers presented with urinary tract infection at admission, and the another 17 had positive history of recurrent infections of urinary system. Ten participants in the study had neurogenic bladder because of myelomeningocele.

Stone analysis and urine assessment

Composition of stones was analyzed by laboratory commercial test (DiaSys Diagnostic Systems GmbH, No 131399990351, Holzheim, Germany) assessing the presence and relative proportions of the seven most frequent natural chemical components. The stone phase was considered to be the major component if it reached at least 50% of the total calculus composition. Four to eight weeks after passing/retrieving the stones and recovery from urinary infection, if present, the 24-hour urine collections were provided while patients were on their usual diet and fluid intake. After voiding, urine samples were kept refrigerated at 4 °C and all measurements were conducted at the end of collection periods within 4 h. Urine assessment included volume, pH and daily excretions of calcium, oxalate, uric acid, cystine, creatinine, phosphate, magnesium and citrate. Urinary metabolites were assessed in an identical manner to that described in our previous publication [13]. Participants and their legal guardians gave informed consent for participation in the procedures, and the study was approved by the ethical committee of the Medical University of Bialystok.

Statistical analyses

The statistical analysis was performed by Statistica, version 10.0 PL (StatSoft Inc., Tulsa, OK, USA). Kruskal–Wallis testing was performed to evaluate differences among the predominantly CaOx, CaP and $MgNH_4P$ stone groups for a given urinary parameter, and Mann–Whitney test was used for comparisons of two groups. Differences were considered statistically significant if $p < 0.05$. Correlations between proportional stone constituents and a given urinary parameter were made using the Spearman test. The r values of correlation coefficients $\leq$0.35 were considered to represent weak a relationship, 0.36–0.67 moderate association and 0.68–1.0 strong correlation [14].

Results

Kidney stone analyses revealed that the vast majority of stones presented mixed composition. The most common chemical combinations were CaOx and CaP admixed with small amount of uric acid (38%) followed by biminerals formed of CaOx and CaP (30%). All infection stones revealed some admixture of metabolic components. Qualitative

Table 1 Reported different combinations of analyzed stone components.

Number of patients	Stone composition
51	CaOx — CaP — UA
40	CaOx — CaP
13	CaOx — $MgNH_4P$ — UA
10	CaOx — $MgNH_4P$ — CaP
10	CaOx
6	CaOx — $MgNH_4P$
3	CaOx — $MgNH_4P$ — CaP — UA
1	CaP — $MgNH_4P$
1	Cystine — CaOx

Table 2 Chemical stone components with respect to frequency of occurrence and range of content.

Stone component	Number of stones — total	Number of stones — main component	Range of content	Median
CaOx	134 (99%)	99 (73%)	5—100%	75%
CaP	105 (77%)	13 (9%)	2—84%	15%
$MgNH_4P$	33 (24%)	18 (13%)	8—83%	46%
UA	67 (49%)	0	2—20%	6%
Cystine	1 (0.7%)	1 (0.7%)	95%	95%

compositions of 135 stones reported by laboratory are given in Table 1.

Calcium oxalate was the most prevalent component included in all but one calculi. We found 10 homogenous and 89 made principally of CaOx stones. Calcium phosphate was the second more abundant chemical admixture found in 105 excrements followed by struvite determined in 33 patients. Crystalline material of 67 patients contained rudimentary amounts of UA. Only one stone consisted of cystine and was not included in further analyses. In four stones containing three or more components, none reached 50% of total composition. Chemical stone components with respect to number of patients and range of content are presented in Table 2.

The majority of our patients presented with urinary metabolic disturbances according to reference values for children [15]. Hypercalciuria (>4 mg/kg/24 h) was found in 90 patients (66%), hypocitraturia (<400 mg/g creatinine) in 85 (63%), hyperoxaluria (>0.5 mmol/1.73 m^2/24 h) in 65 (48%) and cystinuria (>75 mg/1.73 m^2/24 h) in one. None of the participants presented with hyperuricosuria (>815 mg/1.73 m^2/24 h).

Comparison of urine volumes, pH and daily urinary excretions of calcium, oxalate, citrate, uric acid, magnesium and phosphate presented by subgroups forming predominantly CaOx, CaP and $MgNH_4P$ stones are presented in Fig. 1.

Urinary pH was most acid in the subgroup of patients forming predominantly CaOx stones and was significantly lower than that of CaP and $MgNH_4P$ stone formers (median pH 6.11 vs. 6.79 and 6.74, respectively). Additionally, patients with major CaOx stone fractions demonstrated significantly higher calciuria, oxaluria and magnesuria rates when compared with stones mainly composed of CaP and $MgNH_4P$. Patients with predominant CaP stone fraction presented higher uricosuria when compared with CaOx

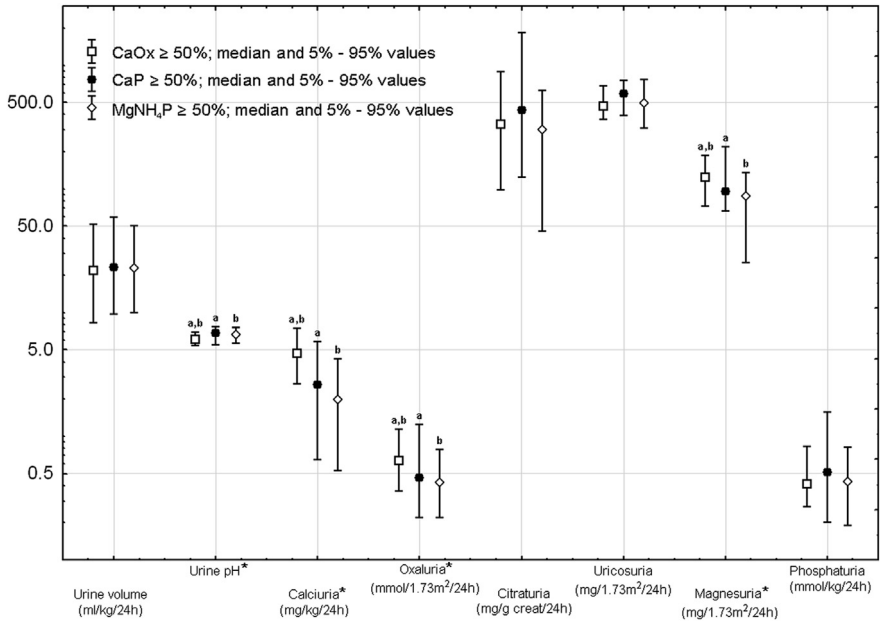

Figure 1 Comparison of subgroups forming predominantly calcium oxalate, calcium phosphate and struvite stones. The Kruskal—Wallis analysis of variance was performed among the predominantly CaOx, CaP and $MgNH_4P$ stone groups for a given urinary parameter. Differences were statistically significant ($p < 0.05$; indicated by *) for pH of urine, calciuria, oxaluria and magnesuria. The Mann—Whitney *U* test was used for comparing two subgroups. Significant differences are marked with letters: [a]CaOx ≥ 50% vs. CaP ≥ 50%; [b]CaOx ≥ 50% vs. $MgNH_4P$ ≥ 50%; [c]CaP ≥ 50% vs. $MgNH_4P$ ≥ 50%.

stones and phosphaturia when compared with both CaOx and $MgNH_4P$ stones.

The calculi content of CaOx showed strong correlation with calciuria ($r = 0.735$) and moderate with oxaluria, magnesuria and acidification of urine ($r = 0.516$, $r = 0.436$ and $r = -0.388$, respectively). The percent content of $MgNH_4P$ revealed distinctly reverse and weaker relationships with regard to above urinary parameters. The CaP stone proportion presented low correlations: positive with alkaline urine and phosphaturia rate and negative with calciuria and oxaluria. The urinary citrate, uric acid and phosphate excretions did not significantly correlate with any proportional stone fractions (Table 3).

Discussion

Although many papers have considered urinary stone composition and concomitant urinary metabolic disturbances in adults, only few studies have focused exclusively on a pediatric population [10,11].

Our study revealed that the vast majority of kidney stones in children represent mixed calculi, evidenced by major and minor stone components. We found that 54% of stones consisted of three components, 35% were composed of two minerals, 8% were monominerals, and 3% were formed of four constituents.

By comparison, a study in Germany based on over 70 000 adult urinary stones showed that 44% consisted of two minerals, 34% were monominerals, 22% of stones were made of three constituents, and 0.7% excrements consisted of four or more components [16]. Our study confirms that pediatric kidney stones are made of a larger number of constituents when compared with published data on adulthood calculi.

Calcium oxalate

There was a definite predominance of CaOx in upper urinary tract stones. It was present in all except one stone, and was a predominant fraction of 73% calculi. The percent of CaOx in stones rose in parallel, as could be expected from physical chemistry, with increasing calciuria, oxaluria, and acidification of urine. We also revealed modest positive correlation with urinary magnesium excretion (Table 3).

Table 3 The correlations between the percentage of stone components and evaluated urinary parameter.

	CaOx (%)	CaP (%)	$MgNH_4P$ (%)
Calciuria	0.735*	−0.188*	−0.503*
Citraturia	0.022	0.064	−0.108
Oxaluria	0.516*	−0.147	−0.466*
Uricosuria	−0.057	0.050	0.048
Magnesuria	0.436*	−0.107	−0.242*
Phosphaturia	−0.031	0.111	−0.062
pH of urine	−0.388*	0.105	0.271*

Spearman's rank correlation coefficients were calculated for each pair of chemical stone component and urinary parameter, *$p < 0.05$.

So far, the role of magnesium in CaOx crystallization has not been fully elucidated. Although magnesium salts are commonly regarded important inhibitors of crystallization, under certain conditions of supersaturation they may presumably operate as promoters of the process [17]. Thus, the role of magnesium in calcium oxalate stone formation deserves further research.

Calcium phosphate

Calcium phosphate was a frequent admixture detected in 77% of stones, but was the major fraction in only 9% of calculi. Calcium phosphate stones are formed when urinary CaP saturation is elevated, mainly because of the alkaline milieu of urine (pH > 6.3) [4,5]. Some reports suggest that calcium phosphate supersaturation is higher in children when compared with adults because of higher pH of urine [7,9].

In our study, the children with predominant CaP stones also presented with significantly higher pH when compared with CaOx stone formers. They presented higher uricosuria when compared with CaOx stones and phosphaturia when compared with both CaOx and $MgNH_4P$ stones (Fig. 1).

However, the correlation coefficients of CaP stone content with pH of urine and urinary risk factors were very low and thus of unclear clinical significance.

Struvite

Struvite stones, a mixture of magnesium ammonium phosphate, are formed when the urinary tract is infected with bacteria that produce a specific enzyme, urease [18]. We found that 24% of stones contained variable amounts of $MgNH_4P$, whereas in 13% it was the major phase. Thirteen children suffering from $MgNH_4P$ stones presented with urinary tract infection at hospital admission, and the other 17 had positive history of recurrent infections of the urinary system. Ten children whose stones were made principally of $MgNH_4P$ have had neurogenic bladder. Subjects with struvite stones tended to be younger in relation to other subgroups. It may be explained by more common infections of the urinary tract in younger children. We did not observe female preponderance in this subgroup of stones, as has been reported elsewhere [12,18]. We revealed moderate inverse relationships of $MgNH_4P$ stone content with calciuria and oxaluria rates, and weak positive correlation with urine pH (Table 3). Interestingly, the urinary magnesium was the lowest among all subgroups. Presumably, $MgNH_4P$ precipitation *in vivo* could have lowered post-renal concentration of urinary magnesium in these individuals [19]. These pre-analytical factors are unavoidable and might lead to changes in excreted element concentration.

Despite relatively low urinary calcium, oxalate and UA in this subgroup of patients, all stones made of $MgNH_4P$ also had a variable component of CaOx, CaP or UA (Table 1). Admixture of CaP could be explained by increased urine pH enabling its precipitation, whereas admixture of the latter is difficult to clarify. We are not able to adjudicate whether other types of stones became secondarily infected with urea-splitting micro-organisms, ensuing secondary struvite stone formation, or, primarily, infection stones were

encrusted with metabolic minerals. Children with struvite stones presented with low citrate excretion, have been reported elsewhere, probably because of degradation of urinary citrate by bacterial enzymes [20].

Uric acid

Uric acid stones are uncommon in childhood, and their prevalence continuously increases with age [5,6]. In our study, neither the 24-hour urinary uric acid excretion was elevated nor pure uric acid stones identified. However, small fractions of UA, mostly not exceeding 10% of total stone composition, were noted in almost half of the stones. This phenomenon is likely to be primarily related to circadian fluctuations in uric acid excretion and, more importantly, in acidification of urine, because precipitation of UA results mainly from low urine pH (pK = 5.5) [21,22].

Uric acid crystals may facilitate development of urinary calcareous stones by forming a nidus for their heterogeneous crystallization [23]. Nevertheless, our study did not include the microscopic assessment of the fine inner structure of calculi, therefore, limiting the possibility to determine the role of UA in calcium stone development. The correlations between percentage of a stone's UA with studied urinary risk factors were not presented as they appear sparsely reliable, mainly because of both extremely small amounts found in the stones and a narrow range of UA content.

The study is limited ultimately by the single method used in the assessment of stone composition. The chemical method has no capacity to differentiate crystalline forms of stone components that could provide an additional insight into structure and potential relationships [16,24]. The other point is the small population studied especially with regard to calcium phosphate and struvite stones. Finally, considering geographical and ethnicity-related differences reported in the topic, we are aware that our data might be affected by region-specific nutritional and lifestyle habits.

In summary, in children, the vast majority of kidney stones are complex: 54% consisted of three components, 35% were composed of two minerals, 8% were monominerals, and 3% were formed of four constituents. Calcium oxalate was the major component of 73% stones, followed by struvite (13%) and calcium phosphate (9%). Uric acid was present in almost half of stones, but in rudimentary amounts. All struvite stones had also a variable metabolic component. The calculi content of CaOx showed positive correlations with calciuria, oxaluria and magnesuria, and negative correlation with urine pH. The percent content of $MgNH_4P$ revealed distinctly reverse and weaker relationships with regard to the above urinary parameters. The CaP stone proportion presented low correlations with urinary risk factors. The urinary citrate, uric acid and phosphate excretions did not significantly correlate with any proportional stone fractions.

Conclusions

Calciuria, oxaluria, magnesuria, and low urine pH exerted the biggest influence on calcium oxalate content in pediatric renal stones. The relationships of urinary risk factors with calculi calcium phosphate content were of unclear clinical significance. Urinary citrate excretion did not significantly correlate with kidney stone composition in children.

Conflict of interest

None.

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None.

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