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ORIGINAL PAPER

Association between the metabolic profile of urolithiasis in children with idiopathic hypercalciuria and the composition of the stone assessed by infrared spectroscopy

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ABSTRACT

Introduction: Urolithiasis is an increasingly common condition. Each patient after stone passage should have stone analysis performed. Every child with a urinary stone should be given a complete metabolic evaluation, and the stone analysis is an essential component of it. The aim of the study was to establish the relation between the metabolic profile of urolithiasis in children with idiopathic hypercalciuria and the composition of the excreted stone.

Material and methods: The study included 26 children with urolithiasis (aged 1–17 years) from whom stones were obtained for the analysis. The urine pH and the 24-hour urine excretion of calcium, phosphorus, magnesium and oxalate as well as spot urinalysis including ratio of crystalloids to creatinine from the second voided urine sample of the day were assessed. Urinary stones were analyzed by infrared spectroscopy. The relation between the metabolic data and the stone type was then analyzed, taking into account two types of minerals: stones with a predominance of calcium oxalate dihydrate (weddellite) and calcium oxalate monohydrate (whewellite).

Results: No correlation was found between the individual serum metabolic parameters of the patient and the composition of excreted stones. Substantially lower urinary excretion of phosphates, oxalate, magnesium and lower urinary pH were found in the group with predominant weddellite stones. A reduced value of each of these 4 variables increased more than sixfold the chance of diagnosing urolithiasis with stone composed of over 60% weddellite.

Conclusions: The urinary metabolic profile is associated with the composition of renal stones estimated in infrared spectroscopy in children with idiopathic hypercalciuria. The coexistence of several urinary excretion anomalies improves the prediction of the composition of the stones.

KEY WORDS:

children, urolithiasis, infrared spectroscopy, calcium oxalate.

INTRODUCTION

Urolithiasis is an increasingly common disease both in the adult and child population. Population studies on the epidemiology of urolithiasis have not yet been performed in the group of pediatric patients. However, local surveys carried out in individual countries indicate an upward trend. Studies by Routh et al. and Ward et al. conducted in the United States, based on hospital databases, showed an increase in the incidence of kidney stones in children

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from 18.4 children per 100,000 hospitalizations in 1999 to 65.2 cases per 100,000 hospitalizations in 2011 [1, 2].

According to the recommendations of the European Society of Urology, each patient diagnosed with urolithiasis should have the chemical composition analysis of at least one stone excreted from the urinary tract spontaneously or removed by surgery. The kidney stone analysis is one of the essential components of the metabolic diagnosis of the causes of urolithiasis. Such diagnostics should be carried out in each child diagnosed with urolithiasis. It is also recommended in adult patients with recurrent stones, high intensity of deposit formation (multiple deposits, occurring in both kidneys) or symptoms (other than only the presence of a stone) suggesting the presence of a systemic disease [3].

All pediatric patients with urolithiasis should undergo metabolic diagnostics which consists of blood and urine biochemical tests. They may allow one to determine the metabolic disease responsible for the formation of deposits or define the risk factors contributing to the patient's urolithiasis [4].

Therefore, in addition to metabolic studies, the analysis of urinary stones is a necessary step in the diagnosis of the possible etiology of stone formation in a patient. It is an important part of the diagnostic procedure, especially for rare types of urolithiasis [5]. In some cases, metabolic disease associated with stone formation is not recognized by standard metabolic testing, while a stone may contain a specific component that allows a clear diagnosis [6].

Kidney stones may be composed of calcium oxalate or less often of calcium phosphates (both account for 85% of cases). They may consist of uric acid (5%) or struvite – magnesium ammonium phosphate (< 10%), which occur in patients with recurrent or chronic inflammation of the urinary tract. The most rare are cystine deposits (< 2%) in patients with genetic cystinuria [7].

Stones in the urinary tract are most often formed from calcium oxalate (about 65–80% of all deposits), which can be identified as two main crystalline phases: calcium oxalate monohydrate (whewellite, COM) or less common calcium oxalate dihydrate (weddellite, COD) [8, 9].

There are several methods to identify urinary stones, but the most accurate methods are X-ray diffraction and infrared spectroscopy. The latter method is now widely used worldwide (approximately 300,000 stone analyses per year).

These methods are able to identify stones composed of calcium oxalate and calcium phosphate, as well as non-calcium stones such as cystine, 2,8-dihydroxyadenine, xanthine, uric acid, urates, methyl-1-uric acid, struvite, proteins, lipids or drugs. Only in 30% of patients do stones have a single chemical component. Stones can remain in the urinary tract for months or even years. Therefore, they are usually made of several different components. However, most reports concerning the composition of renal stones focus on the main component [6].

Renal stone formation is the result of a complex process involving metabolic, anatomical factors and presence of infection. More than 70% of stones in children contain calcium oxalate. In formation of this type of deposits super-saturation of calcium (hypercalciuria) and oxalate (hyperoxaluria) or decreased concentration of inhibitors, such as citrate (hypocitraturia) or magnesium (hypomagnesuria), play the major role. The comparison between metabolic profile of the patient and stone analysis provided evidence that COM crystals are related to hyperoxaluria, while COD crystals are mainly related to hypercalciuria [10–12].

The aim of the study was to establish the relationship between the metabolic profile of urolithiasis in children and the composition of the excreted stone.

MATERIAL AND METHODS

The study involved 26 children with urolithiasis associated with idiopathic hypercalciuria who were under the care of our center and had been diagnosed before the study. The age of the patients ranged from 1 to 17 years. All patients included in the study excreted the stone from the urinary tract spontaneously either by shock wave lithotripsy or other urological intervention. The patients remained on the usual age-appropriate diet.

All participants were given a complete metabolic evaluation. It included blood analysis for: creatinine, sodium, potassium, chloride, calcium, magnesium, uric acid, phosphorus, alkaline phosphatase, 25-hydroxyvitamin D and parathyroid hormone as well as capillary blood gas test. Urinalysis included spot urinalysis and culture, urine pH profile and specific weight. There was also performed 24-hour urine collection for calcium, phosphorus, magnesium, oxalate, uric acid, citrate and creatinine clearance, excluding younger children who did not control their voiding. The excretion norms in the 24-hour urine collection are presented in Table 1 [4, 13]. All the patients underwent a spot urinalysis for ratio of crystalloids to creatinine from the second voided urine sample of the day.

Urinary stones were analyzed by infrared spectroscopy using the Shimadzu Fourier Transform Infrared Spectrophotometer IRTracer-100.

The relation between the metabolic data and the stone type was then analyzed, taking into account two types of minerals: stones with a predominance (> 60%) of calcium oxalate dihydrate (weddellite) and stones with a predominance of calcium oxalate monohydrate (whewellite).

STATISTICAL ANALYSIS

Investigated continuous data are presented as mean with standard deviations and median with interquartile range (IQR). Categorical variables are shown as numbers with the percentage occurrence. The normality of the data distribution was checked with the Shapiro-

TABLE 1. Excretion norms in 24-hour urine collection

24-hour urine collection	Norm
Creatinine	16–30 mg/kg/24 hours
Uric acid	< 12 mg/kg/24 hours or < 815 mg/1.73 m^2 BSA
Calcium	1–4 mg/kg/24 hours
Phosphate	15–20 mg/kg/24 hours
Magnesium	> 1.8 mg/kg/24 hours
Oxalate	< 45 mg/1.73m^2 BSA regardless of gender
Citrate	> 0.92 mmol/1.73 m^2 BSA for boys and > 1.32 mmol/1.73 m^2 BSA for girls

BSA – body surface area

Wilk test. The t-test was used to estimate the differences between variables with normal distribution. Otherwise, the Mann-Whitney test was calculated. For the association analysis between dichotomized and continuous variables the point-biserial correlation test was performed. Significantly associated variables in the univariate logistic regression analyses were tested in ROC analysis to determine the best cut-off point (point closest to 0.1 method) for the probability of identifying weddellite stone occurrence. The double-sided $p < 0.05$ was considered significant. For the parameters of the first ten participants, the Pearson correlation analysis was performed, and then the sample size was estimated. Urinary stone weddellite content was correlated with urinary excretion of magnesium ($r = -0.644$, $p = 0.044$), uric acid ($r = -0.668$, $p = 0.035$), oxalate ($r = -0.851$, $p = 0.002$) and nearly with phosphates ($r = -0.581$, $p = 0.078$). To achieve a significant association between urinary oxalate and phosphate excretion and urinary stones' weddellite content, the sample size was estimated at 26 (for the power of the test = 0.9). For missing data, pairwise deletion was used. Statistical analyses were performed using Statistica software v. 12.0 (StatSoft Inc., Cracow, Poland).

RESULTS

Table 2 presents baseline characteristics of examined children. In 17 of them stones were found, with a predominance of weddellite (65.5%), in 6 with a predominance of whewellite (23%), and in 3 of them the stones were composed of substances other than calcium oxalate (11.5%). In the three patients, data from 24-hour urine collection were lost.

In the time of the study hypercalciuria was confirmed in 10 patients, hyperoxaluria in 9 patients. In both groups the composition of excreted stones was dominated by weddellite. The composition of renal stones depending on the confirmed metabolic disorders in patients is presented in Table 3.

No correlation was found between the individual serum metabolic parameters of the patient and the composition of excreted stones.

Substantially lower urinary excretion of phosphates (9.07 ±3.85 vs. 15.47 ±7.46 mg/24 hours; $p = 0.042$), oxalate (0.428 ±0.275 vs. 0.547 ±0.169 mg/24 hours; $p = 0.057$), magnesium (0.086 ±0.062 vs. 0.131 ±0.088 mg magnesium/mg creatinine; $p = 0.040$), and lower urinary pH (5.60 ±0.66 vs. 6.27 ±0.85; $p = 0.048$) were found in the group with predominant weddellite stones. In the correlation analysis, only these four variables were significantly associated with the occurrence of predominant weddellite stones (Table 4).

The sum of the incidence of urinary excretion of phosphates, oxalates, and magnesium below the minimal reference value and urinary pH ≤ 6 can result in a range from 0 to 4. In the univariate logistic regression analysis, this sum of lower urinary metabolic profile values was significantly associated with the occurrence of predominant weddellite stones (odds ratio 6.794; 95% CI: 1.371–33.661; $p = 0.019$). Thus, a reduced value of each of these 4 variables increased more than sixfold the chance of diagnosing urolithiasis with stone composed of over 60% of weddellite. In the performed ROC analysis, the coincidence of 3 of 4 investigated lower urinary metabolic profile values had the highest predictive properties (84.6% sensitivity and 70.0% specificity, AUC 0.862; $p < 0.001$) for predominant weddellite stones identification (Table 5, Figure 1).

DISCUSSION

Urolithiasis has become a more common disease in children in recent years. It has been agreed that diagnostic examination is necessary for every child experiencing even a single kidney stone event. Furthermore, we know that analysis of the stone obtained after spontaneous stone passage or intervention is one of the most important diagnostic measures.

The existing data in the literature indicate that the major role in formation of calcium oxalate stones is played by super-saturation of calcium (hypercalciuria) and oxalate (hyperoxaluria) or decreased concentration of inhibitors, such as citrate (hypocitraturia) or magnesium (hypomagnesuria) in the urine.

TABLE 2. Baseline characteristics of examined children

Variable	N	Mean	Standard deviation (SD)	Median	Interquartile range (IQR)
Age [years]	26	14.73	18.18	12.00	8.00
Phosphate/24 hours[n]	23	11.85	6.43	10.71	8.41
Magnesium/24 hours	23	2.51	3.13	1.80	0.83
Uric acid/24 hours	23	9.23	3.52	8.08	3.60
Creatinine/24 hours[n]	23	19.31	3.75	18.29	4.00
Oxalate/24 hours[n]	24	0.47	0.24	0.46	0.29
Citrate/24 hours[n]	26	1.45	0.83	1.24	1.31
Calcium/24 hours	23	3.57	1.87	3.31	2.93
Calcium/creatinine ratio	26	0.19	0.26	0.13	0.10
Magnesium/creatinine ratio	26	0.10	0.07	0.08	0.05
Phosphate/creatinine ratio	26	0.49	0.31	0.46	0.44
Magnesium/calcium ratio	26	0.80	0.81	0.56	0.41
Uric acid/creatinine ratio[n]	26	0.24	0.09	0.22	0.14
Serum sodium[n]	26	140.11	1.53	140.00	2.00
Serum magnesium[n]	26	2.06	0.17	2.10	0.20
Serum calcium[n]	26	10.07	0.45	10.10	0.70
Serum chloride	26	101.80	1.26	102.00	2.00
Serum urea	26	23.61	7.10	23.00	7.00
Serum creatinine[n]	26	0.55	0.18	0.60	0.30
Serum phosphate[n]	26	4.48	0.68	4.40	1.10
Serum uric acidn	26	4.21	1.25	4.10	1.90
Serum potassium[n]	26	4.49	0.33	4.50	0.60
Blood pH[n]	26	7.39	0.01	7.39	0.02
Blood bicarbonate[n]	26	24.36	1.63	23.90	2.30
Urin pH	26	5.88	0.80	5.75	1.50
Vitamin D[n]	26	29.92	11.32	29.85	18.40
Parathyroid hormone[n]	26	24.42	7.11	22.55	10.90
Weddellite %	26	64.15	39.26	70.50	59.00

[n]Variable with normal distribution.

TABLE 3. Composition of renal stones depending on the confirmed metabolic disorders

Parameters	Hypercalciuria *N* = 10	Hyperoxaluria *N* = 9
Predominance of weddellite, *n* (%)	7 (70)	4 (44.5)
Predominance of whewellite, *n* (%)	2 (20)	3 (33.3)
Non-calcium oxalate, *n* (%)	1 (10)	2 (22.2)

Our study showed no association between higher excretion of calcium and the composition of excreted stone. We found no correlation with hyperoxaluria, but the study revealed a correlation with the reduced excretion of oxalate.

Literature data indicate that hyperoxaluria may lead to urinary supersaturation of calcium oxalate and crystal formation, contributing to urolithiasis. It is considered the main risk factor for calcium oxalate urolithiasis. Supersaturation of calcium oxalate is 10 times more dependent on a rise in urinary oxalate than on an equivalent rise of urinary calcium concentration [14, 15]. We found no information in the literature about any association with calcium oxalate dihydrate stones and low oxalate excretion.

We did not observe any correlation with decreased concentration of citrate in the urine, although citrate is known as a naturally occurring inhibitor of the formation of calcium stones. It binds ionized calcium and reduces calcium saturation, inhibits accumulation of calcium oxalate and thus impedes the growth of calcium oxalate stones [16].

We found an association between low magnesium to creatinine ratio and calcium oxalate dihydrate stones. However, this relation in our study was not found in 24-hour urine collection for magnesium.

Magnesium competes with calcium for binding to oxalate. The result is magnesium oxalate, which is more soluble in the urine than calcium oxalate. Moreover, magnesium reduces oxalate absorption both in the gastrointestinal and urinary tract [17]. However, there has been much controversy in recent years regarding the role of magnesium in the formation of urinary stones. Some studies show that magnesium prevents hyperoxaluria by the described mechanism, while other investigations do not support this finding [18, 19]. Eisner *et al.* in their study found that the rate of hyperoxaluria was decreased in higher magnesium excretion in urine [19]. The study by Schwartz *et al.* [18] revealed that patients with hypomagnesuria excreted significantly less oxalate, citrate, calcium, uric acid, and sodium in their urine, which is consistent with the findings of Tavasoli *et al.* [20], who investigated the association between magnesium excretion and other urine metabolites. Tavasoli *et al.* suggested that since rich sources of magnesium contain a high amount of oxalate at the same time, it might explain why urine magnesium level showed a direct association with urine oxalate [20]. Another study by Bonny *et al.* showed that urinary magnesium directly inhibited renal calcium absorption, leading to hypercalciuria [21].

Another component that has been regarded as a risk factor for stone formation and recurrence is excretion of phosphate. Several studies of phosphate excretion have shown that patients with idiopathic hypercalciuria have hyperphosphaturia or renal phosphate leak. However, the frequency of renal phosphate leak in these patients remains unclear [22–25].

It is known that coexistence of hypercalciuria and hyperphosphaturia leads to formation of calcium phosphate complexes that can result in nephrolithiasis [25]. Nevertheless, another mechanism is also taken to consideration. Some investigations showed that calcium phosphate crystals can interact with the renal epithelium, create sites for crystal attachment and then grow into calcium phosphate stones or promote sites for calcium oxalate crystal formation [24, 26].

Our study did not show any relation between hypercalciuria and hyperphosphaturia. We found a correlation between weddellite formation and low excretion of phosphate that is not supported by any available literature.

TABLE 4. Correlations of urinary metabolic profile variables with predominant weddellite stones occurrence

Urine	Correlation coefficient	Significance
Calcium [mg/kg/24 hours]	–0.045	$p = 0.837$
Phosphates [mg/kg/24 hours]	–0.504	$p = 0.014$
Magnesium [mg/kg/24 hours]	0.094	$p = 0.670$
Urinary acid [mg/kg/24 hours]	–0.316	$p = 0.142$
Creatinine [mg/kg/24 hours]	0.125	$p = 0.570$
Oxalate [mg/1.73m^2/24 hours]	–0.447	$p = 0.033$
Citrate [mmol/1.73m^2/24 hours]	–0.126	$p = 0.568$
Ca/creatine [mg/mg]	–0.145	$p = 0.509$
Mg/creatinine [mg/mg]	–0.419	$p = 0.046$
P/creatinine [mg/mg]	–0.086	$p = 0.698$
Uric acid/creat [mg/mg]	–0.257	$p = 0.237$
Urine pH	–0.431	$p = 0.040$

The last association that we found was between lower values of urine pH and calcium oxalate dihydrate stones. The pH of the urine is treated as a major factor in the formation of many stones [4].

It was believed so far that alkaline urine reduces solubility of calcium phosphate products whereas acidic urine pH favors precipitation of organic stone such as uric acid and cystine. At the same time, urine pH in calcium oxalate urolithiasis was considered to have little effect on formation of these stones apart from the mechanism of heterogeneous crystallization (when one type of crystal acts as a template, thereby promoting crystallization of a second type of crystal) [27]. However, recent studies have suggested that acid pH increases calciuria by inhibiting TRPV5/6-mediated calcium reabsorption in the distal nephron. Bonny *et al.* conclude that renal calcium absorption can be negated by high luminal pH [21]. Also Wagner and Mohebbi emphasize in their review that local and systemic acidosis increases urinary excretion of calcium, which leads to higher risk for crystallization [28]. These findings are consistent with the results of our study.

Our research did not show any correlation between the hyperoxaluria and calcium oxalate monohydrate crys-

TABLE 5. Predictive properties of lower urinary metabolic profile values in the identification of weddellite stones

LUVS	Sensitivity	Specificity	Accuracy	AUC (95% CI)	Significance
0	1.000	0.000	0.565	0.862 (0.712–1.000)	$p < 0.001$
1	1.000	0.200	0.652		
2	1.000	0.400	0.739		
3	0.846	0.700	0.783		
4	0.385	1.000	0.652		

AUC – area under curve, CI – confidence interval, LUVS – lower urinary metabolic profile values sum.

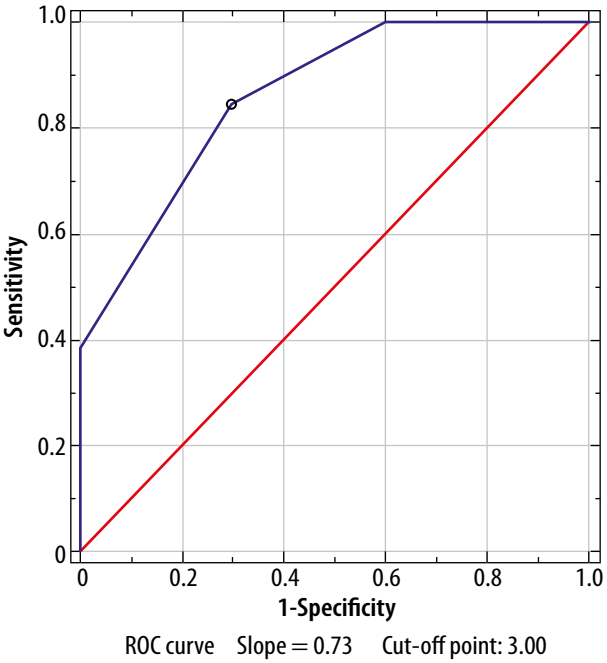

FIGURE 1. ROC for the sum of the 4 variables below the threshold

tals. It also did not show any association between hypercalciuria and calcium oxalate dihydrate crystals. However, literature data indicate that whewellite crystals are related to hyperoxaluria, while weddellite crystals are mainly related to hypercalciuria [10–12]. Our results may not show this relation due to the small group of examined patients.

Our study showed a very new correlation, not described before, between the metabolic parameters of the patient and the composition of excreted stones. Our findings are controversial because they mostly do not correspond with the existing literature data.

There are a few studies that try to show a new approach to metabolic evaluation of stone formers. For example, Turudic *et al.* stated that the rarely used calcium independent oxalate/(citrate x glycosaminoglycans) ratio serves as a high specificity marker for idiopathic calcium oxalate urolithiasis [29]. Another study of Wang *et al.* revealed potential urinary biomarkers using ultra-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry (UPLC-Q-TOF/MS), which may help to improve future metabolic evaluation of urolithiasis [30].

Idiopathic hypercalciuria is a complex disorder that is probably affected by both environmental and genetic factors. Correlations found in our study may arise from the complexity of this disease and its heterogeneous pathogenesis, which is not fully understood.

Our results may contribute to a new approach to the metabolic causes of urolithiasis. Perhaps we should consider them from a different perspective and reanalyze the mechanisms leading to urinary stone formation.

Our study was conducted on a small group and it only provides a new look at the problem of idiopathic hypercalciuria and urolithiasis. Further studies are needed to determine these new metabolic correlations.

CONCLUSIONS

The urinary metabolic profile is associated with the composition of renal stones estimated in infrared spectroscopy in children with idiopathic hypercalciuria. The coexistence of several urinary excretion anomalies improves the prediction of the composition of the stones.

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DISCLOSURE

The authors declare no conflict of interest.

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