Composition of Urinary Stones in Children: Clinical and Metabolic Determinants in a French Tertiary Care Center

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Abstract

The aim was to describe the composition of stones of pediatric patients, to illustrate current epidemiological trends in pediatric urolithiasis.

Clinical and metabolic data from all pediatric patients with at least one stone that was analyzed by Fourier Transformed Infrared Spectroscopy (FTIR) in the *Hospices Civils de Lyon s Civils de Lyon* between 2013 and 2017 were retrospectively collected. A total of 111 patients (sex ratio 1.4:1) were included; their median [IQR] age was 7.5 [3.1-10.5] years. The main component of stones was calcium oxalate [weddellite for 34 (31%) stones, whewellite 23 (21%)], calcium phosphate [carbapatite 32 (29%), brushite 6 (5%), amorphous calcium phosphate 3 (3%)], struvite 5 (5%), cystine 4 (4%), uric acid 2 (2%), and ammonium acid urate 2 (2%). A total of 20 (18%) stones were pure and 24 (22%) were infectious. Carbapatite stones were the most frequent in patients < 2 years and calcium oxalate stones in patients > 2 years old. Metabolic abnormalities (most frequently hypercalciuria) were found in 50% of tested patients and in 54% of patients with infectious stones. Congenital anomalies of the kidney and/or urinary tract (CAKUT) or neurogenic bladder was present in 9/24 (38%) patients with infectious stones and 12/16 (76%) patients with bladder stones.

Conclusion: This study confirms that calcium oxalate stones are the most frequent among pediatric patients, which could reflect the nutritional habits of predisposed patients. In contrast, infectious stones are less frequent and occur mostly in association with anatomic or metabolic favoring factors.

Introduction

Lithogenesis occurs when urine is supersaturated with stone-forming salts (1, 2). Multiple factors can cause this supersaturation and some of them are dramatically impacted by the overall health status, notably by hydration and nutrition (3). Pediatric cases of urolithiasis are less common than adult ones, but their incidence has increased over the past decades in high-income countries (4). Changes in nutritional habits are thought to partially explain this increase (5). Some genotypes, especially in children, are considered as additional risk factors for lithogenesis (alleles implicated in innate metabolic pathways, e.g. in the vitamin D, calcium, and phosphate metabolic pathways) (6). Recent papers have also suggested that intestinal absorption of stone promoters is influenced by the microbiome diversity (7). In parallel, progress in the management of urinary tract infections (UTI) have led to a decreased frequency of infectious stones (8).

Urolithiasis is responsible of recurrent pain and UTI in children (9). Moreover, patients with stones present a 2-fold increased risk of developing chronic kidney disease (CKD) compared to the general population (10). This risk is even higher in monogenic stone diseases such as primary hyperoxaluria or cystinuria, which are responsible for at least 10% of urolithiasis in children. Because they require specific management and therapies, they must be diagnosed as early as possible (6).

As the epidemiology of urolithiasis is constantly evolving, analyzing the composition of stones is crucial to better understand the determinants of lithogenesis in order to adapt prevention and management strategies. Thus, the aim of the present study was to describe the composition of stones of pediatric patients in a tertiary University center and their clinical and biological presentation, to illustrate the current epidemiological trends of urolithiasis in children.

Methods

Patients

Patients under 18 years with a urinary stone that was analyzed by Fourier-transform infrared (FTIR) spectroscopy between 1/1/2013 and 12/31/2017 in the biochemistry department of the *Hospices Civils de Lyon (HCL)* were retrospectively identified. Patients followed in the tertiary nephrology and/or urology pediatric units of the *HCL* were included. Some patients underwent multiple stone analyses, only the first spectroscopic analysis during the study period was considered. To be able to evaluate the changes in the composition of stones with age, a classification similar to the one proposed by Daudon *et al.* was used (11): patients were categorized into five different age groups (group 1: ≥0 and < 2 years, group 2: ≥2 and < 5 years, group 3: ≥5 and < 10 years, group 4: ≥10 and < 15 years, and group 5: ≥15 years). The present retrospective study was approved by the local IRB (*Comité d'Ethique des Hospices Civils de Lyon*, session 6/7/2018).

Data collection

Clinical, radiological, and metabolic data were retrospectively collected from electronic medical records. Urine and blood metabolic evaluation was performed when patients were referred to a pediatric nephrologist, mostly within 6 months before or after the spectroscopic analysis. Urinary tests were performed on 24-hour urine collection if possible, or on urinary samples. Patients presenting with cystine stones underwent a targeted evaluation of cystinuria.

The 2009 revised Schwartz formula was used to estimate Glomerular Filtration Rate (eGFR) (12). Normal urinary values for urinary calcium, oxalate, citrate, and uric acid were expressed as solute/creatinine ratio and depended on age, as previously referenced (13–15). Hyperphosphaturia was defined when the ratio of maximum transport of phosphate to eGFR (TmP/GFR) was lower than 1.15 mmol/L (16), normal value for urinary cystine/creatinine ratio was < 30 µmol/mmol.

FTIR spectroscopy

The composition and morphology of stones were determined using the morphoconstitutional analysis (1, 17). Briefly, after a macroscopic and a microscopic description, calculi were crushed and diluted with potassium bromure for analysis by Fourier Transformed Infrared Spectroscopy (FTIR). The composition was deciphered by comparison on spectral databases. Stones were described depending on their main component, for example a 'carbapatite stone' refers to a stone for which the main component is carbapatite.

Infectious stones definition

According to Daudon *et al.*, stones were considered infectious when they contained struvite, amorphous calcium phosphate, whitlockite, or carbapatite with a carbonatation rate > 15% (17).

Statistical analysis

Quantitative variables were expressed as median [interquartile range, IQR]. They were compared with non-parametric Mann-Whitney U tests. Qualitative variables were expressed as count (percentage), they were compared using χ^2 tests. A p-value < 0.05 was considered significant.

Results

Patient characteristics

Out of the 5782 stones analyzed by FTIR spectroscopy during the study period in the biochemistry department of the *HCL*, 202 (4%) belonged to patients under 18 years. Among them, 111 were followed in the tertiary nephrology and/or urology pediatric units of the *HCL* and were therefore included in the study; their sex ratio was 1.4:1, and their median [IQR] age at the time of spectroscopy evaluation was 7.5 [3.1–10.5] years. Family history of urolithiasis was known for 83 patients and a first-degree history was reported for 19 (23%) of them. A total of 26 (23%) patients had a congenital anomaly of the kidney and urinary tract (CAKUT), among them 6/26 (23%) had a Mitrofanoff cystostomy. A serious pre-existing medical condition was present for 18 (16%) patients: 9 had neurological impairment, 2 had chronic digestive inflammatory disease, 3 had metabolic disorders, 3 had hemato-oncological diseases, and 1 underwent cardiac transplantation. One (1%) patient had moderate CKD (eGFR 49.5 mL/min per 1.73 m²) and 4 (4%) mild CKD (eGFR between 77 and 87 mL/min per 1.73m²).

Clinical presentation

There was a significant difference in the main symptoms leading to urolithiasis diagnosis between age groups (p = 0.003): the proportion of UTI was the highest (58%) in the first age group (group 1) and decreased with age, the proportion of renal colic and pain symptoms increased with age and was the highest (73%) in the oldest age group (group 5). The proportion of fortuitous diagnosis reached about 20% in each age group (Fig. 1). Initial or intercurrent UTIs were present in 54 (49%) patients.

For 16 (14%) patients stones were located in the bladder only, for 90 (81%) patients at least one stone was in the kidney and/or the ureter (upper urinary tract, UUT), and for 5 (5%) stones were not localized. Among the 90 UUT stones, 21/90 (23%) were bilateral, and 5/90 (6%) were associated with bladder stones.

Stones were collected spontaneously [33(30%)], after extracorporeal shockwave lithotrypsy [36 (32%)], endoscopic extraction [33 (30%)], or during a laparoscopy or open surgery [9 (8%)] that was often scheduled for another reason.

Composition of stones

The main component of stones was calcium oxalate [weddellite for 34 (31%) stones, whewellite 23 (21%)] and calcium phosphate [carbapatite 32 (29%), brushite 6 (5%), amorphous calcium phosphate (ACP) 3 (3%)]. Struvite was predominant in 5 (5%) stones, cystine in 4 (4%), and uric acid and ammonium acid urate (AAU) each in 2 (2%) (Fig. 2a**)**. A total of 20 (18%) stones were pure, 47 (42%) contained 2 and 44 (40%) contained at least 3 components. Uric acid stones were found in 2 (2%) children who received multiple therapies for severe inflammatory bowel disease and complex cardiac surgery. There was no drug-containing stone.

The composition of stones seemed to be different between age groups (Fig. 2a) but not between sexes (Figs. 2b-c): the proportion of carbapatite stones decreased with age from 8/19 (42%) in group 1 to 1/11 (9%) in group 5, the proportion of calcium oxalate stones increased with age from 7/19 (37%) in group 1 to 9/11 (82%) in group 5. More precisely, the proportion of weddellite stones was similar in all groups (21 to 39%) whereas whewellite stones were absent in the youngest groups of age, were found in group 3, and were predominant in groups 4 and 5. There was a significant difference in the composition of stones between age groups relative to the 3 most frequent components (whewellite, weddellite, and carbapatite, p = 0.004; **Table 1**).

Metabolic Evaluation

Complete metabolic urinary evaluations were performed for 67 (60%) patients and targeted evaluations for 3 (3%) patients who had cystine stones to confirm cystinuria. Out of the 70 patients tested, 35/70 (50%) had at least one metabolic abnormality (Fig. 2d). A total of 6/70 (9%) patients displayed elevated urinary cystine/creatinine ratio: from 150 to 370 µmol/mmol for the 3 patients with cystine stones, and from 34 to 57 µmol/mmol for 3 patients with stones of another composition.

A total of 15 patients underwent a genetic screening driven by clinical and biological findings, and pathogenic mutations were identified in 7/15 (47%) of them: 4 had cystinuria, 1 had primary hyperoxaluria, and 2 harboured heterozygous mutations in the *SLC34A3* gene encoding the sodium/phosphate co-transporter Npt2c.

Bladder stones

For 16 (14%) patients stones were located in the bladder only; their sex ratio was 3, their median [IQR] age was 10.3 [4.2–13.7] years and they tended to be older than patients with kidney/ureter stones (7.4 [2.5–11.1] years; p = 0.06). Among these 16 patients, 12 (75%) had anatomic factors favoring urinary stasis: 11 had CAKUT (including 6 bladder exstrophies) and 1 had neurogenic bladder (Fig. 3a). Among the 4 patients without urinary stasis factor, 1 had cystinuria, 2 had excessive calcium intakes during their first years of life, and 1 had infectious stone. The median [IQR] age of the 12 patients with bladder stones who had anatomic factors favoring urinary stasis was 11.5 [9.0-14.7] years, which was significantly higher than the median [IQR] age of the remaining 4 patients (3.7 [3.3–5.4] years; p < 0.001). A history of UTI was present for 12/16 (75%) patients (Fig. 3b). There was a significant difference in the composition of

stones between bladder stones and UUT stones in terms of main component (p = 0.008; Fig. 3c). Struvite was predominant in 2 (13%) stones, and 8 bladder stones (50%) contained struvite.

Infectious stones

A total of 24 (22%) stones were considered as infectious: the main component was carbapatite in 14/24 (58%) infectious stones, struvite (5/24, 21%), ACP (3/24, 13%), and AAU (2/24, 8%); 17 (71%) contained struvite. The sex ratio of patients with infectious stones was 3, their median [IQR] age was 7.4 [3.7–11.0] years. A history of UTI was encountered in 17 (71%) patients with infectious stones and 9 (38%) had associated conditions of urinary stasis. The median [IQR] age of patients with CAKUT or neurogenic bladder was 10.9 [6.5–13.4] years, they were significantly older than patients without these anatomic factors (6.2 [3.3–9.2] years; p = 0.04). Out of the 24 infectious stones, 8/24 (33%) were located in the bladder, 15/24 (63%) in the UUT, and 1/24 (4%) was not localized.

Out of the 13 patients with infectious stones who underwent metabolic analysis, 7/13 (54%) had at least one metabolic abnormality, the most common were hyperoxaluria (3/7), hypercalciuria (2/7), and hypocitraturia (2/7).

A metabolic evaluation was performed for 20 of the 32 patients with predominant carbapatite stones and revealed a metabolic abnormality for 13/20 (65%) of them, regardless of whether carbapatite was considered infectious or not.

Discussion

The present study confirmed the trend observed over the last decades reporting an increase of the proportion of calcium oxalate stones and a decrease of the proportion of infectious stones (11,18). Less than a fifth of the stones analyzed were pure, suggesting that stone formation was multifactorial in most cases. There was a high proportion of bladder stones in this cohort.

Calcium oxalate stones were predominant, which is consistent with recent reports (19–22). Weddellite and whewellite stones are found in conditions of hypercalciuria or hyperoxaluria, respectively, or both. These conditions can be influenced by dietary factors and intestinal absorption and are more likely to be encountered in patients with predisposing innate urinary conditions (18). Calcium excretion is increased by high intakes of sodium, diets rich in animal proteins (23,24), and high fructose intake (25). Changes over the last decades towards such diets might therefore be responsible for an increased incidence of calcium oxalate stones in children close to the one found in adults.

Although influenced by food intake, oxalate urinary excretion is particularly affected by intestinal oxalate absorption that is increased with digestive inflammation (26). Additionally, the gut microbiome is less diverse in pediatric calcium oxalate-stone formers, with particularly low levels of oxalate-degrading bacteria (7). Alterations of the microbiome diversity could explain the association found between frequent use of antibiotics and stone disease (27).

The formation of AAU stones is also influenced by nutrition but they occur in conditions of undernutrition, notably in case of phosphate-deficient diets, chronic diarrhea, and dehydration (28) and are a major component of endemic bladder stones frequent among young boys in low income countries (20). These stones gradually disappear as health conditions improve (28). As expected, AAU stones were rarely identified in the cohort herein, while they account for 30% of the pediatric stones in low income countries (19,20).

While uric acid stones caused by a low urinary pH and/or excessive purine intakes are common in adults particularly in case of obesity, they remain rare in children (18). Children have a slightly higher urine pH than adults that does not favor uric acid crystallization (29). This could explain why the well-established association between obesity and urolithiasis in adults remains discussed for children (5). Uric acid stones were found herein only in 2 patients who were receiving multiple treatments.

The influence of inherited factors on pediatric urolithiasis varies according to the composition of stones. Cystine stones occur for instance only in case of congenital cystinuria, an autosomal recessive condition (30). The influence of genetic predispositions for the formation of calcium oxalate or calcium phosphate stones is more variable. Some rare monogenic disorders, such as primary hyperoxaluria (31), or Dent's disease (32), induce a high lithogenic susceptibility. Recent data have revealed that a causative monogenic mutation could be detected in up to 20% of idiopathic urolithiasis and/or nephrocalcinosis (33). Due to an increased risk of CKD in monogenic stone diseases, genetic analyses are particularly indicated in case of early start, familial history, recurrent, and/or bilateral stones. However, innate risks for stone formation are frequently driven by a polygenic susceptibility or a heterozygosity in known genes. Moreover, some risk factors that were considered as purely environmental and cultural, such as dietary habits, might be partially inherited (34,35). Metabolic inherited predisposition such as hypocitraturia or hypercalciuria might also vary regionally (14,36).

Besides dietary and inherited metabolic factors, infections also play an important role. Struvite stones are always caused by infection (1). Their proportion was lower compared to historical cohorts, particularly among males younger than 2 years: only 7% stones contained struvite, whereas Daudon *et al.* has reported 38% of struvite-containing stones (11). This decrease in infectious stones partially explain why the historical male predominance in pediatric urolithiasis is currently less clear. Over the last fifty years, the trend towards an equilibration of the sex ratio in high income countries has been illustrated by three successive British cohorts, reporting a decrease from 2.9 to 1.3 of the sex ratio between 1966 and 2015 (37–39). The sex ratio found in the present study was close to the one reported in the most recent study (37) but it remains higher among patients with infectious stones.

Unlike struvite stones, carbapatite stones – about one third of the stones identified herein – are not always caused by UTIs (1): they form in alkaline urines induced by either urea-splitting bacterial infection or defect in urine acidification. When patients were screened for metabolic abnormalities, 65% of carbapatite stones were associated with metabolic abnormalities, sometimes leading to a specific diagnosis and management such as thiazide treatment in case of hypercalciuria resistant to dietary

measures. It seems therefore essential to systematically screen patients for metabolic abnormalities even in case of UTI in order to optimize therapeutic strategies, especially for older patients without associated CAKUT and for patients with carbapatite stones for which the carbonatation rate is < 15%.

In addition, both the lower proportion of infectious stones and the increased median age of patients with infectious stones compared to historical cohorts (11) likely reflect an improvement in the management of UTIs and CAKUT in young children over the past decades. The development of infectious stones in older patients can be partly explained by infectious stones occurring later in life in patients with severe CAKUT. Another consequence of the high proportion of complex CAKUT was the elevated proportion of bladder stones (14%) compared to recent studies from high income countries (mostly < 10%) (37,40,41). Endemic bladder stones caused by undernutrition are nevertheless still common in some low income countries where they represent up to 50% of the stones below 2 years (42). In the present cohort, bladder stones occurred in different conditions: patients were older and most of them had CAKUT. As previously published, bladder stones in conditions of complex CAKUT are not always infectious and patients must be screened for metabolic factors (43).

Last, the high number of minimal invasive extraction modes reflects the continuous improvement in pediatric urology, and particularly the miniaturization of equipment, and a will to preserve renal development by limiting potential adverse effects of “open” surgical procedures.

The present study has strengths: it is one of the largest series on pediatric urolithiasis in high income countries of the last decade, and data collection is the most recent. However, it also suffers from limitations, mainly because of its retrospective design. Since patients were seen either in nephrology or in urology, a large proportion of patients did not undergo metabolic evaluation, despite current guidelines recommending a systematic complete metabolic evaluation in case of pediatric urolithiasis (44).

In conclusion, this retrospective cohort provided a recent picture of renal stone disease among children followed in a pediatric University hospital in France. The composition of stones has evolved over the last decades: infectious stones are less frequent and occur mostly in association with anatomic or metabolic factors. In contrast, calcium oxalate stones are more frequent, which could be explained by changes in nutritional habits. The high proportion of bladder stones was associated with complex CAKUT. As factors are often combined, a systematic metabolic evaluation of pediatric stone formers remains nevertheless crucial, even when the infectious etiology seems clear. Genetic screening should be considered in case of suggestive situations.

Declarations

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Conflicts of interest/Competing interests The authors have no relevant financial or non-financial interests to disclose

Availability of data and material The datasets analyzed during the current study are available from the corresponding author

Code availability not applicable

Authors' contributions All authors made substantial contributions to the conception of the work and to the interpretation of data. They revised it critically and approved the version to be published. They agree to be accountable for all aspects of the work.

Ethics approval This retrospective and strictly observational study was approved by the local IRB (*Comité d'Ethique des Hospices Civils de Lyon*, session 6/7/2018).

Consent to participate not applicable

Consent for publication not applicable

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Tables

Table 1 Most frequent main components according to age groups

Only the three main components whewellite (W1), weddellite (W2) and carbapatite (CA) were considered (N=89 patients)". Data are expressed as total number of patient (% in age group). Differences were significant between age groups (p=0.004) using a χ^2 Test.

	Main Component		CA	Total
Age group	**W1**	**W2**		
1	0 (0%)	7 (47%)	8 (53%)	15 (17%)
2	0 (0%)	9 (53%)	8 (47%)	17 (19%)
3	7 (28%)	8 (32%)	10 (40%)	25 (28%)
4	11 (50%)	6 (27%)	5 (23%)	22 (25%)
5	5 (22%)	4 (12%)	1 (3%)	10 (11%)
Total	**23**	**34**	**32**	**89**

Figures

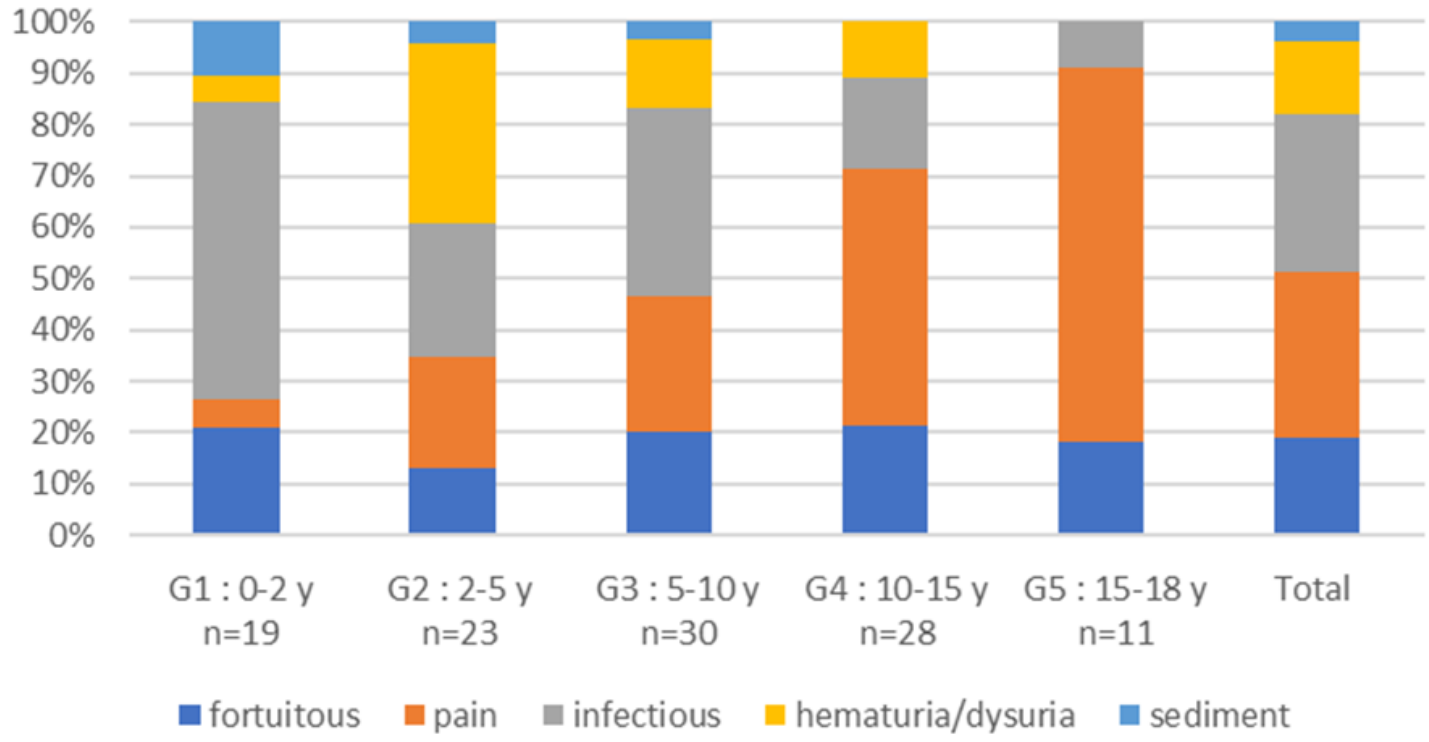

Figure 1

Clinical presentation Clinical presentation according to age groups. Data are presented as % of total number of patients of each age group. Proportions were compared using Chi Square test: p = 0.03

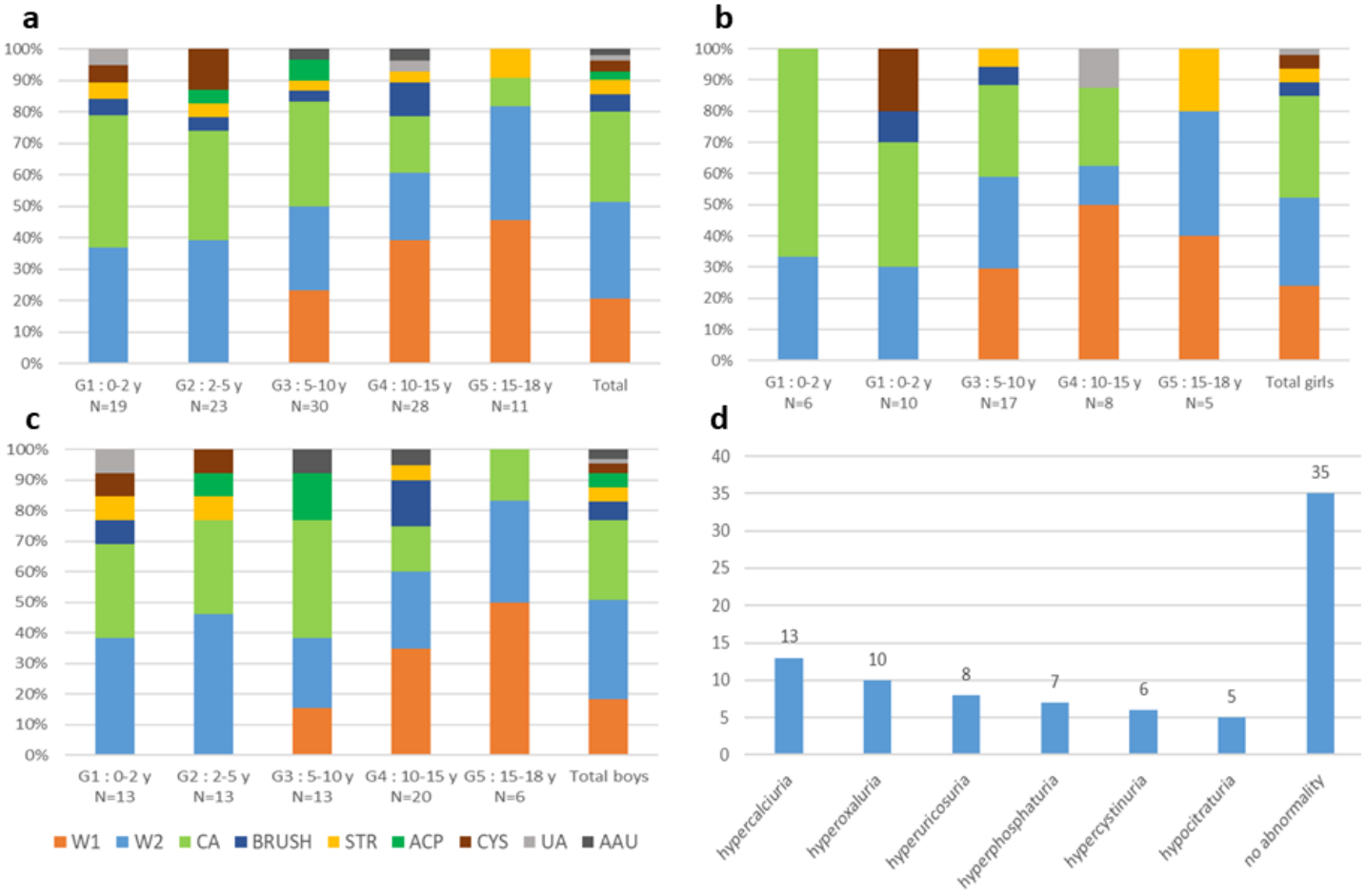

Figure 2

Main components according to age groups and metabolic abnormalities Main components of urolithiasis according to age groups (all patients (a), girls (b), boys (c)) and metabolic abnormalities ((d), 70 patients with complete or targeted metabolic evaluation). Data are presented as % of total number in each age group (a-c) and total number of patients (d). Statistical analyses were not performed for 2a-c because of a low number of patients in each group. For 2d the total number exceeds 70 as some patients displayed more than one abnormality. W1 = Whewellite, W2 = Weddellite , CA = Carbapatite, BRUSH = Brushite, STR = Struvite, ACP = Amorphous Calcium Phosphate, CYS = Cystine, UA = Uric Acid, AAU = Ammonium Acid Urate, G1 = group 1

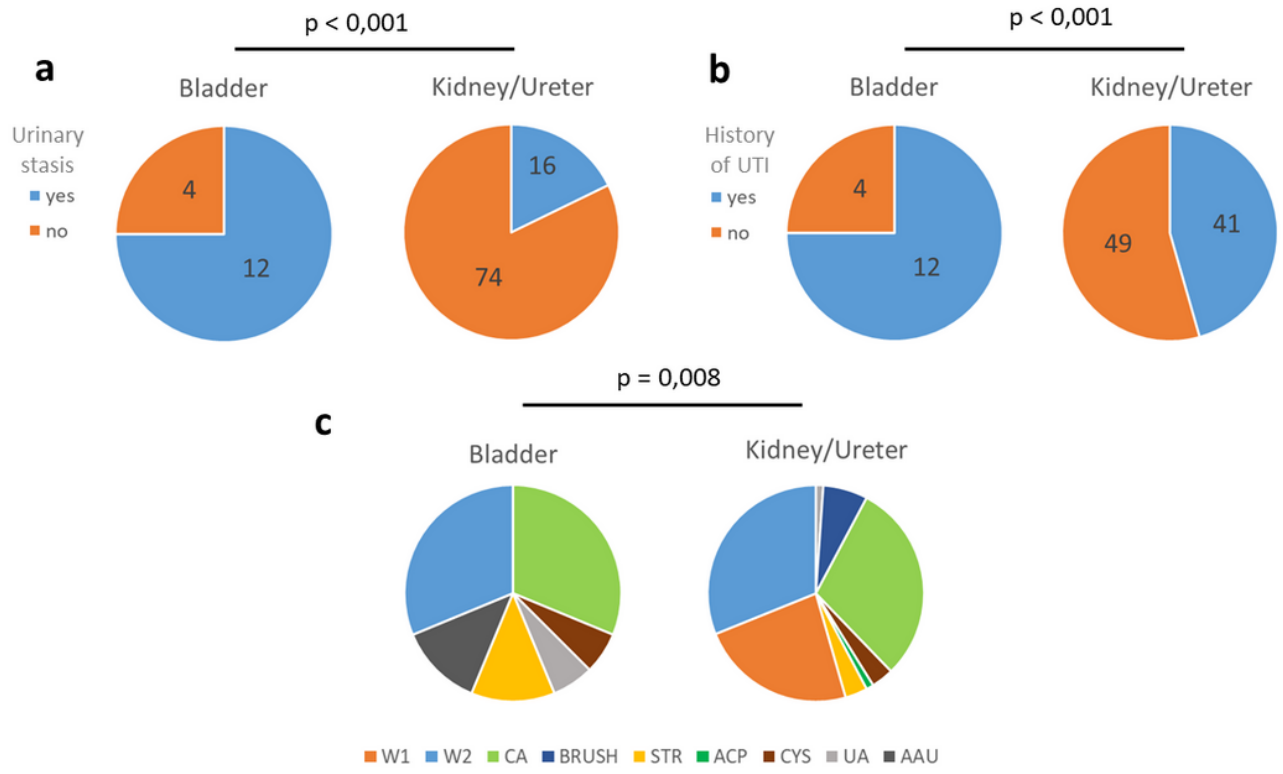

Figure 3

Bladder stones: clinical determinants and main components Bladder stones compared to other localizations (UUT and not localized): history of CAKUT (a), history of UTI (b) and main components (c). W1 = Whewellite, W2 = Weddellite , CA = Carbapatite, BRUSH = Brushite, STR = Struvite, ACP = Amorphous Calcium Phosphate, CYS = Cystine, UA = Uric Acid, AAU = Ammonium Acid Urate