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Urolithiasis

# Influence of Overweight on 24-Hour Urine Chemistry Studies and Recurrent Urolithiasis in Children

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**Purpose:** We investigated the influence of overweight on 24-hour urine chemistry studies and recurrent urolithiasis (UL) in children.

**Materials and Methods:** A retrospective cohort study was designed to assess children who presented with UL at a pediatric institution between 1985 and 2010. We calculated body mass index percentile (BMIp) adjusted for gender and age according to the 2007 Korean Children and Adolescents Growth Chart and stratified the children into 3 BMI categories: lower body weight (LBW, BMIp≤10), normal BW (NBW, 10<BMIp<85), and upper BW (UBW, BMIp≥85). Twenty-four hour urine chemistry studies (urine volume, creatinine, calcium, oxalate, citrate, and pH) were compared between the 3 BMIp groups. Univariate and multivariate analyses were performed to assess independent risk factors for stone recurrence.

**Results:** A total of 125 patients were included. The age of the patients in the NBW group was older than that of patients in the LBW group, but 24-hour urine chemistry studies did not differ significantly between the three groups. Mean urine citrate levels were lower (0.273±0.218 mg/mg/d vs. 0.429±0.299 mg/mg/d, $p<0.05$) and the incidence of hypocitraturia was higher (81.5% vs. 45.7%, $p<0.05$)) in the recurrent stone former group. In the univariate analysis, hypocitraturia and acidic urinary pH were risk factors, but in the multivariate analysis, only hypocitraturia was a risk factor for stone recurrence (hazard ratio, 3.647; 95% confidence interval, 1.047 to 12.703). In the Kaplan-Meier curve, the hypocitraturia group showed higher recurrence than did the normocitraturia group ($p<0.05$).

**Conclusions:** Unlike in adults, in children, overweight adjusted for gender and age was not associated with 24-hour urine chemistry studies and was not a risk factor for recurrent UL. Hypocitraturia was the only risk factor for UL in children.

***Key Words:*** *Body mass index percentile; Overweight; Pediatric urolithiasis*



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## INTRODUCTION

Urolithiasis (UL) in pediatric patients is relatively rare, and the prevalence in children varies from 2 to 2.7% [1]. Recent studies have shown that the annual incidence is increasing in different populations [2]. Several factors predispose children to developing UL, and metabolic and genitourinary abnormalities are particularly important; these are often associated with diet, environmental factors, and infectious causes. UL is associated with considerable morbidity and high recurrence rates.

Data about UL in children have increased in recent years. Most children with urinary UL have underlying metabolic abnormalities, and hypercalciuria is the most prevalent [3]. Other metabolic risk factors vary in frequency according to different series [4]. Some metabolic alterations that have been described include hypocitraturia, hyperuricosuria, hyperoxaluria, renal tubular acidosis, and cystinuria [5].

The relationship between body size and risk of UL in

adults has been studied extensively [6]. Abnormal urinary excretion of calcium, oxalate, and uric acids and abnormally low urinary pH have been linked to increasing body weight and body mass index (BMI) [7]. Increasing BMI is a risk factor for abnormal 24-hour urine chemistry studies in adult stone formers and healthy controls without a history of UL [8]. Despite these data in adults, however, little is known about the relationship between BMI and risk factors for UL in children. Moreover, little is known about the relationship between BMI and the recurrence of UL in children. It can be difficult for clinicians to predict which children are at risk for stone recurrence after the first stone episode. We evaluated 24-hour urine chemistry results in children with a history of UL and examined possible correlations between BMI and risk factors for UL. We analyzed BMI and 24-hour urine chemistry results in the recurrence group and compared the results with those in a cohort without recurrence to determine which patients may need more aggressive dietary and pharmacological therapy after the first stone episode.

## MATERIALS AND METHODS

### 1. Study design

A retrospective cohort study was designed to assess all children less than 18 years of age who presented with UL at a single pediatric institution between 1985 and 2010. Inclusion criteria were presumed calcium-based renal or ureteral stones on the basis of a stone analysis or radiographic imaging, with at least one 24-hour urine chemistry study conducted after the initial diagnosis. Exclusion criteria were bladder stones, radiolucent stones (i.e., presumed uric acid), obstructive uropathy, chronic renal insufficiency, reconstructed lower urinary tract requiring clean intermittent catheterization, or patients who were taking thiazide diuretics.

The diagnosis of UL was made clinically and was confirmed in all cases by radiographic imaging, such as ultrasonography, excretory urography, or noncontrast computerized axial tomography. Treatment was individualized and included watchful waiting for spontaneous passage, if suitable, or surgical intervention if obstruction or sepsis was present or if a trial of passage had failed. Follow-up imaging after passage or surgical treatment included plain abdominal radiography and renal ultrasound.

Pre-evaluation medical treatment was not controlled, but patients generally were advised to begin nonspecific therapy. This therapy included recommendations to increase fluid intake to achieve a urine output of at least 1 to 2 ml/kg per hour. No restriction was made regarding the intake of calcium-containing foods (e.g., milk, cheese). BMI was calculated as weight in kilograms divided by the square of height in meters ($kg/m^2$) from self-reported patient height and weight values.

### 2. Urine collection

Subjects were given a prescription for a urinary metabolic evaluation to be performed at home or at the hospital. One or two 24-hour urine collections were performed via spontaneous voiding. Internal quality assurance controls were adhered to in the laboratory per standard protocols to assess for undercollection and to validate the volume measurement. The metabolic evaluation included standard urinary indexes such as volume, creatinine, calcium, oxalate, citrate, and pH. The laboratory methods used to evaluate the 24-hour urine samples were calcium-atomic absorption spectrophotometry, a citrate-citrate lyase enzymatic method, the oxalate-enzymatic method, the creatinine-alkaline picrate method, urinary Becker volume-volumetric measurement by visual analysis, and urinary pH-reagent test strips with a methyl red and bromothymol blue indicator system.

### 3. Statistical analysis

Urine chemistry results were adjusted for 24-hour urinary creatinine excretion to account for variations in patient size, and urine volume was adjusted for age. Although there is no universally accepted cutoff for normal daily urinary citrate excretion in children, a value $<400$ mg/g creatinine was used to define hypocitraturia. Hypercalciuria was defined as urinary calcium excretion $>4$ mg/kg and hyperoxaluria as oxalate excretion $>0.57$ mg/kg. A low urinary volume was considered when at least one of the samples had a 24-hour urinary volume $<15$ ml/kg, and acidic urine was defined as a pH $<6.0$ [9].

We measured the BMI for each patient at the time of diagnosis of UL and then calculated BMI percentile (BMIp), which adjusts for gender and age according to the 2007 Korean Children and Adolescents Growth Chart [10]. Patients were stratified into three BMI categories as follows: lower body weight (LBW, BMIp$\leq$10), normal BW (NBW, 10$<$BMIp$<$85), and upper BW (UBW, BMIp$\geq$85). The 24-hour urine chemistry study results were adjusted for urinary creatinine and were evaluated among the three BMIp categories by analysis of variance, and the incidences of hypercalciuria, hypocitraturia, hyperoxaluria, low urinary volume, and acidic urinary pH were compared among the three BMIp groups by use of the chi-square test.

Patients who were observed for at least 1 year were stratified into two groups of either no recurrence or recurrence according to the recurrence of UL during the follow-up period. The 24-hour urine chemistry study results adjusted for urine creatinine were evaluated between the no recurrence and recurrence groups by using the Student's t-test, and the incidences of hypercalciuria, hypocitraturia, hyperoxaluria, low urinary volume, and acidic urinary pH were compared between groups by using the chi-square test. Univariate and multivariate analyses with the Cox proportional hazard model were performed to assess independent risk factors for stone recurrence. Each of the categorical independent variables was included in the model. This analysis generated an adjusted hazard ratio (HR) and 95% confidence interval (CI) for each independent variable while controlling for all variables

simultaneously. Variables with a 95% CI that did not include 1.0 were believed to exclude the null hypothesis and were considered significant risk factors for developing recurrent stones. We used the Kaplan-Meier curve to determine associations among BMIp, 24-hour urine chemistry, and stone recurrence, and any differences in the survival curves were compared by the log-rank test. SPSS ver. 14.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis, and p-values less than 0.05 were considered statistically significant.

## RESULTS

We indentified 189 pediatric patients with stones at our institution, and 125 patients were included in this study. Table 1 shows the baseline patient characteristics. The median age of the patients was 10 years (range, 1 to 18 years), 79 patients (63%) were boys, and the common sites for stones were the kidneys, upper ureter, and lower ureter (32.8%, 31.2%, and 25.6%, respectively). Seventy-four patients (58.4%) were observed for more than 1 year, and the median follow-up period was 4.95 years (range, 1 to 20 years). During the follow-up, 27 (36.5%) of 73 patients experienced a recurrence, and 10 patients experienced more than one recurrence.

When we stratified the patients into the LBW, NBW, and UBW groups, the number of patients in the groups was 28, 71, and 26, respectively. The patients in the NBW group were older than the patients in the LBW group, but the 24-hour urine chemistry study results adjusted for urine creatinine did not differ significantly among the three groups. Moreover, the incidences of hypercalciuria, hypocitraturia, hyperoxaluria, low urinary volume, and acidic urinary pH were not significantly different (Table 2).

When we stratified the 73 patients who were observed for at least 1 year into two groups of either no recurrence or recurrence, there were 46 and 27 patients in the groups, respectively. The mean follow-up periods in the no recurrence and recurrence groups were 4.09±3.48 and 6.41±4.96 years, respectively, which was not statistically different. The incidences of stone recurrence in the LBW, NBW, and UBW groups were 36.8% (7 of 19), 48.6% (18 of 37), and 11.8% (2 patients of 17 patients), respectively, and the incidences of stone recurrence in the LBW and NBW groups were higher than in the UBW group. The incidence of UBW was lower in the recurrence group than in the no

**TABLE 1.** Patient characteristics

| Characteristic | Value |
|---|---|
| Age (yr) | 10 (1-18) |
| Boy | 79 (63) |
| BMI percentile (%) | 50 (2-98) |
| Stone site | |
| Kidney | 41 (32.8) |
| Ureteropelvic junction | 18 (14.4) |
| Upper ureter | 39 (31.2) |
| Midureter | 3 (2.4) |
| Lower ureter | 32 (25.6) |
| 24-Hr urine chemistry | |
| Sodium (mmol/mg/d) | 0.2 (0.02-1.32) |
| Calcium (mg/mg/d) | 0.18 (0.01-2.80) |
| Citrate (mg/mg/d) | 0.31 (0.03-18.28) |
| Oxalate (mg/mg/d) | 0.03 (0.01-0.36) |
| Urine volume (mg) | 1,300 (200.0-3,900.0) |
| Urine pH | 6.5 (5.0-9.0) |
| Follow-up period (yr) | 4.95 (1-20) |
| No. of recurrences | |
| 0 | 46 (36.8) |
| 1 | 17 (13.6) |
| 2 or more | 10 (8) |
| Unknown | 52 (41.6) |

Values are presented as median (range) or number (%).
BMI, body mass index.

**TABLE 2.** Result of 24-Hour urine chemistry accodring to patient body mass index

| Variable | LBW (n=28) | NBW (n=71) | UBW (n=26) | p-value |
|---|---|---|---|---|
| Age (yr) | 8.21±6.36 | 11.62±5.75 | 9.81±5.72 | 0.031 |
| 24-Hr urine chemistry | | | | |
| Sodium (mmol/mg/d) | 0.19±0.09 | 0.24±0.24 | 0.26±0.23 | 0.628 |
| Calcium (mg/mg/d) | 0.37±0.53 | 0.21±0.21 | 0.20±0.12 | 0.065 |
| Citrate (mg/mg/d) | 0.4±0.23 | 0.39±0.31 | 0.37±0.27 | 0.911 |
| Oxalate (mg/mg/d) | 0.06±0.07 | 0.04±0.04 | 0.05±0.04 | 0.71 |
| Urine volume (mg) | 1,466.43±884.14 | 1,487.89±802.98 | 1,576.92±891.99 | 0.871 |
| Urine pH | 6.78±0.70 | 6.53±0.88 | 7±0.99 | 0.345 |
| Hypercalciuria | 11 (39.29) | 15 (21.13) | 6 (23.08) | 0.166 |
| Hypocitraturia | 13 (46.43) | 38 (53.52) | 16 (61.54) | 0.738 |
| Hyperoxaluria | 17 (60.71) | 27 (38.03) | 12 (46.15) | 0.122 |
| Low urine volume | 1 (3.57) | 12 (16.90) | 6 (23.08) | 0.114 |
| Acidic urinary pH | 9 (32.14) | 28 (39.44) | 7 (26.92) | 0.483 |

Values are presented as mean±SD or number (%).
LBW, lower body weight; NBW, normal body weight; UBW, upper body weight.

recurrence group (33% vs. 7%, $p<0.05$), and mean urinary citrate levels were lower (0.273±0.218 mg/mg/d vs. 0.429± 0.299 mg/mg/d, $p<0.05$) and the incidence of hypocitraturia was higher (81.5% vs. 45.7%, $p<0.05$) in the recurrence group than in the no recurrence group, although other lithogenic factors did not differ significantly among the groups (Table 3).

Univariate and multivariate analyses with the Cox proportional hazard model were performed to assess the independent risk factors for stone recurrence. In the univariate analysis, hypocitraturia and acidic urinary pH were risk factors for stone recurrence, but only hypocitraturia was an independent risk factor for stone recurrence in the multivariate analysis (HR. 3.647; 95% CI, 1.047-12.703) (Table 4).

The Kaplan-Meier survival analysis revealed that the group with hypocitraturia (n=43) had a higher and faster recurrence rate than did the group with normocitraturia (n=30), ($p<0.05$), although other 24-hour urine chemistry values and BMIp were not significantly different (Fig. 1).

**TABLE 3.** Demographic data and 24-hour urine chemistry results in the no recurrence and recurrence groups

| | No recurrence group (n=46) | Recurrence group (n=27) | p-value |
|---|---|---|---|
| Boy | 28 (61) | 21 (78) | 0.138 |
| BMI percentile | | | |
| LBW | 12 (26) | 7 (26) | 0.033 |
| NBW | 19 (41) | 18 (67) | |
| UBW | 15 (33) | 2 (7) | |
| Age (yr) | 10.93±5.6 | 12.81±5.2 | 0.166 |
| 24-Hr urine chemistry | | | |
| Sodium (mmol/mg/d) | 0.230±0.214 | 0.197±0.232 | 0.588 |
| Calcium (mg/mg/d) | 0.293±0.414 | 0.184±0.097 | 0.201 |
| Citrate (mg/mg/d) | 0.429±0.299 | 0.27±0.218 | 0.026 |
| Oxalate (mg/mg/d) | 0.056±0.057 | 0.039±0.005 | 0.202 |
| Urine volume (mg) | 1,426.087±871.891 | 1,712.222±923.444 | 0.190 |
| Urine pH | 6.640±0.764 | 6.473±0.679 | 0.408 |
| Hypercalciuria (≥4 mg/kg/d) | 12 (26.08) | 9 (33.33) | 0.509 |
| Hypocitraturia (≤400 mg/g Cr/d) | 21 (45.65) | 22 (81.48) | 0.001 |
| Hyperoxaluria (≥0.57 mg/kg/d) | 20 (43.47) | 12 (44.44) | 0.936 |
| Low urine volume (≤20 ml/kg/d) | 7 (15.21) | 4 (14.81) | 0.963 |
| Acidic urinary pH (≤6.0) | 14 (30.43) | 11 (40.74) | 0.370 |
| Follow-up period (yr) | 4.09±3.48 | 6.41±4.96 | |

Values are presented as mean±SD or number (%).
BMI, body mass index; LBW, lower body weight; NBW, normal body weight; UBW, upper body weight.

**TABLE 4.** Cox proportional analysis for predictive factors for stone recurrence

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | RR | CI | p-value | RR | CI | p-value |
| BMI percentile | | | | | | |
| LBW | 0.908 | (0.366-2.255) | 0.835 | 1.06 | (0.389-2.889) | 0.909 |
| NBW | - | - | - | - | - | - |
| UBW | 0.352 | (0.080-1.550) | 0.352 | 0.286 | (0.06-1.374) | 0.118 |
| Hypercalciuria (≥4 mg/kg/d) | 0.897 | (0.386-2.086) | 0.801 | 1.311 | (0.505-3.4) | 0.578 |
| Hypocitraturia (≤400 mg/g Cr/d) | 3.907 | (1.168-13.071) | 0.027 | 3.647 | (1.047-12.703) | 0.042 |
| Hyperoxaluria (≥0.57 mg/kg/d) | 1.191 | (0.549-2.585) | 0.658 | 1.586 | (0.598-4.205) | 0.354 |
| Low urine volume (≤20 ml/kg/d) | 1.766 | (0.591-5.276) | 0.308 | 2.033 | (0.551-7.495) | 0.286 |
| Acidic urinary pH (≤6.0) | 2.399 | (1.060-5.427) | 0.036 | 2.056 | (0.856-4.936) | 0.107 |

RR, relative risk; CI, confidence interval; BMI, body mass index; LBW, lower body weight; NBW, normal body weight; UBW, upper body weight.

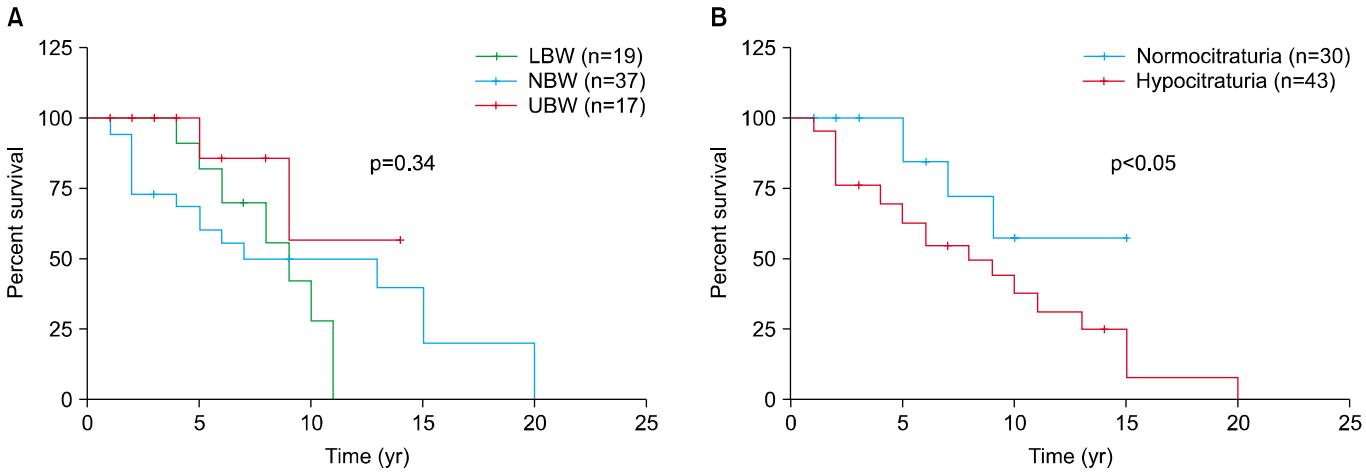


**FIG. 1.** Kaplan-Meier curve estimating the probability of stone recurrence according to patient age and body mass index percentile. LBW, lower body weight; NBW, normal body weight; UBW, upper body weight.

## DISCUSSION

Mounting evidence in the adult literature points to a causal relationship between obesity and urinary stone development. Taylor et al. [11] reported a significantly increased risk between increasing body mass and subsequent kidney stones in three large prospective cohorts. A more recent study of a large commercial administrative claims database supported this finding, showing a significant increased risk of UL in adults with a BMI $>30$ kg/m$^2$ [12]. Siener et al. [13] demonstrated a strong association between obesity and an increased risk for stone formation owing to increased urinary excretion of stone-forming risk factors.

An association between increasing BMI and increasing urinary excretion of sodium, calcium, uric acid, and citrate has been reported [14]. Adult studies have shown that increased BMI values are a risk factor for increased urinary calcium and sodium and decreased urine pH and volume. The role of body mass on metabolic parameters has been explored to explain the biological mechanisms promoting stone formation in overweight and obese individuals. Siener et al. [13] noted that increased BMI affects urinary homeostasis by increasing factors that promote stone formation, such as decreased urinary pH, increased urinary calcium, and increased urinary uric acid excretion. In Korea, Jung et al. [15] demonstrated that each metabolic syndrome (MS) trait including BMI was a significant lithogenic factor compared with other lithogenic factors in 40,687 Koreans at a health promotion center. Moreover, Chang et al. [16] reported that MS at baseline and MS over time were associated with a significantly increased risk of nephrolithiasis and were significantly associated with an increased risk of developing urine acidification at follow-up in 3,872 men who were reexamined by kidney ultrasonography annually or biannually for 8 years.

The influence of obesity on stone recurrence was investigated in 704 Korean stone formers, and this study reported that stone recurrence rates were more frequent in obese stone formers than in nonobese stone formers. Moreover, obese stone formers had a decreased time to stone recurrence [17].

These trends have led some to consider whether a similar association exists in children. However, we found no significant association between BMI and stone disease in the pediatric population. Sarica et al. [18] studied 97 children and compared quantitative 24-hour urine chemistry study results of overweight children (BMI $\geq 25$) with those of controls (BMI $<25$). They found that overweight patients excreted significantly greater amounts of oxalate and calcium and significantly less citrate than did controls, all of which are known risk factors for nephrolithiasis. Obese children have increased urinary metabolic risk factors for stone disease, such as hyperoxaluria. However, BMI increases with age. For example, a BMI of 16 in a 3-year-old boy places him in the 50th percentile, whereas a BMI of 16 in a 14-year-old boy falls in the 5th percentile. Because that study did not adjust for BMIp, however, it is difficult to compare their results with ours. Our analysis was adjusted for age, creatinine excretion, and BMIp to evaluate the association between BMI and 24-hour urine chemistry study results. We measured BMI in each patient and then calculated BMIp, which was adjusted for gender and age according to the 2007 Korean Children and Adolescents Growth Chart [10]. We think that it is very important to adjust these confounding factors by the Korean national growth chart for BMI to identify the effects of overweight and obesity on UL in children. In the largest pediatric case series to date on the role of BMI in the formation of pediatric stones, Kieran et al. [19] found no data to support a direct role for high BMI in the presentation or treatment of kidney stones by using 3 BMI categories according to the Centers for Disease Control and Prevention age-adjusted BMI percentiles for children, including LBW (10th percentile or less), NBW (10th to 85th percentile), and UBW (85th percentile or greater). Also, Kim et al. [20] reported that high body mass was not associated with UL in a matched

case-control study. Thus, we assumed that BMI increases with age, and that children grow annually unlike adults. Moreover, the physical growth of children is different from that of adults, indicating that BMI in adults is commonly fixed, whereas BMI in children could change over time. Therefore, these preliminary findings suggest that the pathophysiology of pediatric stone formation may be distinctly different from that in the adult population, but further large-scaled prospective studies are needed to confirm these results.

Metabolic abnormalities are commonly found in the pediatric stone-forming population, and a full metabolic evaluation is often performed after the first stone episode [21]. Metabolic disorders are present in 12.3 to 96% of children with UL. Idiopathic hypercalciuria is the most frequent urinary metabolic risk factor found and is detected in 40 to 69% of cases [22]. Acar et al. [23] reported the incidence of idiopathic hypercalciuria as the most common factor in 40% of cases. Tefekli et al. [24] found that hypocitraturia is the most prevalent metabolic risk factor in children, and Van Dervoort et al. [2] also observed that hypocitraturia is the most commonly identified metabolic abnormality, which was present in 52% of the children studied between 2003 and 2005. Moreover, children with identified metabolic abnormalities had higher recurrence rates than did those without abnormalities [25]. In our study, hypocitraturia was the only risk factor for pediatric UL and stone recurrence. We believe that our data support the recommendation that all children with UL should undergo a metabolic evaluation and those with positive findings should be followed carefully for evidence of symptomatic or asymptomatic stone recurrence. On the basis of our results, we believe that the effect of obesity on UL in children is different from that in adults and that metabolic problems are more important lithogenic factors than is obesity in children.

There are several limitations to our study. First, it was retrospective in nature and thus is subject to the shortcomings of a nonprospective design and the relatively small number of subjects compared with the adult cohort. Second, the data were somewhat underpowered to stratify the pediatric group by gender or into prepubertal and postpubertal age groups. The pediatric cohort did not include many infants or young children owing to the difficulty of obtaining 24-hour urine collections from non-toilet-trained children. Although we did not include genetic and environmental factors, the ratio of a family history component varies from 12 to 50% in different studies [26]. This may suggest a significant contribution of genetic factors to the pathogenesis of urinary stones.

## CONCLUSIONS

Unlike in adults, overweight, adjusted for gender and age, was not associated with 24-hour urine chemistry results and was not associated with UL in children. Hypocitraturia was a predictive factor for stone recurrence in children. Thus, the physiopathology of UL in children may be different from that in adults, and more prospective studies are needed to better understand the determinants of UL in children.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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