# Calcium-to-Citrate Ratio Distinguishes Solitary and Recurrent Urinary Stone Forming Children

William DeFoor,*,† Elizabeth Jackson, Marion Schulte, Zaheer Alam and John Asplin‡

*From the Children's Hospital Medical Center, Cincinnati, Ohio, and Laboratory Corporation of America® Holdings, Chicago, Illinois (JA)*

Accepted for publication March 23, 2017.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

* Correspondence and requests for reprints: Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave., MLC 5037, Cincinnati, Ohio 45229-3039 (telephone: 513-636-6758; FAX: 513-636-6753; e-mail: Bob.defoor@cchmc.org).

† Financial interest and/or other relationship with AKSM.

‡ Financial interest and/or other relationship with Litholink®.

**Purpose:** The prevalence of urinary stone disease is increasing in children. We previously reported a high rate of urinary metabolic abnormalities, including hypercalciuria and hypocitraturia, in stone forming children. In this study we determined whether calcium-to-citrate ratio could help predict those at risk for recurrent stone formation.

**Materials and Methods:** We conducted a retrospective cohort study to assess calcium-to-citrate ratios in children with urolithiasis. Two 24-hour urine collections were performed. Urinary excretions of calcium and citrate were analyzed, and calcium-to-citrate ratio was calculated. Patients were stratified into solitary and recurrent stone formers and compared to a control group of normal children.

**Results:** We identified 73 solitary and 92 recurrent stone formers. Mean patient age was 13 years for both groups. Gender was well matched. A total of 29 normal children served as controls. Mean calcium-to-citrate ratio was 0.41 in solitary stone formers and 0.64 in recurrent stone formers ($p = 0.02$). Mean value in normal children (0.33) was significantly less compared to recurrent stone formers ($p = 0.002$) and trended lower compared to solitary stone formers ($p = 0.15$). The ratio was abnormally high in recurrent stone formers (70%) compared to solitary stone formers (47%, $p = 0.003$).

**Conclusions:** There are significant differences in urine calcium-to-citrate ratios between solitary and recurrent calcium stone forming children. Solitary stone formers trended higher compared to controls. These findings may allow more precise risk stratification and treatment to prevent recurrent stone episodes.

**Key Words:** nephrolithiasis, urinalysis, hypercalciuria, pediatrics

Urinary stone disease is becoming more common in children.[1,2] We have previously reported a high rate of urinary metabolic abnormalities, including hypercalciuria and hypocitraturia, in stone forming children.[3–5] After presentation of the first stone episode it can be difficult for clinicians to predict which children are at increased risk for stone recurrence. At our multidisciplinary pediatric stone center 24-hour urinary metabolic evaluations are typically obtained after the first stone episode. We have previously demonstrated that increased levels of calcium and citrate are independent risk factors for stone recurrence by multivariate analysis.[5] Some investigators have proposed using a ratio of these 2 indices to help stratify risk, and a recent study suggested a normal cutoff value.[6] In the current study we assessed whether calcium-to-citrate



0022-5347/17/1982-0416/0
THE JOURNAL OF UROLOGY®
© 2017 by American Urological Association Education and Research, Inc.
http://dx.doi.org/10.1016/j.juro.2017.03.125
Vol. 198, 416-421, August 2017
Printed in U.S.A.

ratio could help determine which children may benefit from aggressive medical intervention after the first stone episode. We hypothesized that children with a high calcium-to-citrate ratio would be at increased risk for recurrent stone formation.

## MATERIALS AND METHODS

We designed a retrospective cohort study to assess all patients presenting with nephrolithiasis at a single pediatric institution between 2007 and 2014. Inclusion criteria consisted of presence of a kidney stone and availability of at least one 24-hour urinary metabolic evaluation performed before initiation of pharmacotherapy. Kidney stones were diagnosed based on clinical presentation and confirmed in all cases with radiographic imaging as well as available operative findings and/or crystallographic analysis. Imaging studies included plain x-ray of the kidneys, ureters and bladder, renal ultrasound and/or noncontrast enhanced computerized tomography.

Exclusion criteria were age older than 21 years at evaluation, presence of struvite bladder stones and presence of obstructive uropathy. Patients with a neurogenic bladder and upper urinary tract stones on an optimum regimen of clean intermittent catheterization were not excluded. Clinical management was individualized and included watchful waiting for spontaneous stone passage if deemed appropriate. Surgical intervention was performed if obstruction and/or sepsis was present or if a symptomatic patient had a failed trial of passage with medical expulsive therapy. Followup imaging with plain x-ray of the kidneys, ureters and bladder and/or renal ultrasound was routinely performed after stone passage or definitive surgical treatment.

If a stone fragment was available, stone analysis was performed elsewhere (Beck Laboratories, Indianapolis, Indiana) using standard crystallographic techniques. Medical treatment before the urinary metabolic evaluation was not controlled, but generally patients were advised to begin nonspecific therapy such as increasing fluid intake and decreasing added table salt. No specific restrictions were imposed regarding intake of calcium or oxalate containing foods before the metabolic evaluation. Specific dietary histories were not recorded.

Patients were given an order for two 24-hour urinary metabolic evaluations to be performed at home. The samples were express mailed to an outside central laboratory (Litholink). Metabolic evaluation consisted of standard urinary indices, including calcium and citrate excretion. Internal quality assurance controls were performed in the laboratory to assess for under collection and to validate volume measurement. Specimens with a creatinine excretion of less than 9 mg/kg were considered under collected and excluded from analysis. Followup studies after beginning medical therapy were excluded from the analysis.

Patients were stratified as solitary or recurrent stone formers based on a review of the medical record. The classification was made blinded to the results of the urinary metabolic evaluation. Patients who initially presented with multiple unilateral or bilateral stones were placed into the recurrent group by definition. A cohort of normal children with no known stone disease recruited for a previous study was used as a control group.[3]

Calcium-to-citrate ratio (mg/mg) was calculated for each 24-hour urine sample. The 2 ratios were averaged for inclusion in the final database for analysis. Mean and standard error were then calculated for each group. Median and interquartile range were also evaluated. Univariate analysis between means was performed using a 2-tailed t-test. A statistically significant difference was defined as a p value of less than 0.05. A histogram was evaluated to qualitatively assess the overlap of the groups. Nonparametric statistical testing (Mann-Whitney) was also performed to compare groups. ROC curves were also generated to calculate area under the curve for the study groups.

We reviewed the literature to assess for a normal reference range for calcium-to-citrate ratio in children. No published reference ranges could be found. However, in 1 review of random calcium-to-citrate ratios values above 0.326 seemed to discriminate between hypercalciuric children who formed kidney stones.[6] Therefore, for our study values greater than 0.326 were considered abnormal. Comparison of proportions using Fisher exact test was performed, and statistical significance was defined as a p value of less than 0.05. Statistical analyses were performed using MedCalc® statistical software, version 17.0.

*Patient demographics*

| | Solitary Stone Formers | Recurrent Stone Formers | Controls |
|---|---|---|---|
| No. pts (%): | | | |
| Male | 30 (41) | 41 (45) | 17 (59) |
| Female | 43 (59) | 51 (55) | 12 (41) |
| Mean age (yrs) | 12.6 | 13.1 | 9.6 |
| Mean wt (kg) | 45.8 | 47.0 | 33.8 |

## RESULTS

A total of 73 solitary stone formers and 92 recurrent stone formers were identified. Mean age was 12.7 years for the solitary group and 13.3 years for the recurrent group at metabolic evaluation ($p = 0.2$). Mean body weight was 46.6 kg for the solitary group and 47.2 kg for the recurrent group ($p = 0.8$). Body mass index was similar between study groups (20.3 for the solitary group and 20.5 for the recurrent group). Gender was well matched between the 2 study groups. A total of 29 normal children (56 samples) recruited for a previous study served as controls.[3] The control group was somewhat younger (9.6 years). Demographic data are outlined in the table. Most known stones were calcium oxalate. Prevalence of uric acid stones in our patient population was negligible.

Mean ± SE calcium-to-citrate ratio in solitary stone formers was 0.41 ± 0.04 (median 0.33, IQR 0.23 to 0.41). Mean ± SE calcium-to-citrate ratio in recurrent stone formers was 0.64 ± 0.09 (median

0.46, IQR 0.31 to 0.60). Means of the 2 groups were significantly different, with a p value of 0.02 (fig. 1). In normal children the mean ± SE of 0.33 ± 0.05 (median 0.30, IQR 0.20 to 0.46) was significantly lower than in recurrent stone formers ($p = 0.002$). The control group trended lower but missed statistical significance in comparison to solitary stone forming children ($p = 0.15$). A histogram of recurrent stone formers vs normal controls is presented in figure 2. Nonparametric comparisons between controls and recurrent stone formers, and between solitary and recurrent stone formers revealed similar significant differences between groups (data not shown).

When assessing the groups regarding cutoff value found in the literature, 47% of those in the solitary stone forming group had a value above 0.33, compared to 41% in the normal control group. Of those in the recurrent stone forming group 70% had an abnormally high value. The percentage of those with abnormal values in the recurrent group was significantly higher than in the solitary group ($p = 0.003$) or normal controls ($p = 0.008$).

Comparisons between the groups using ROC curves were performed and are illustrated in figure 3. An optimum cutoff between recurrent stone formers and controls was 0.31, with a sensitivity of 59% and a specificity of 72% ($p = 0.0003$). When comparing solitary to recurrent stone formers, the optimum cutoff was 0.28, with a sensitivity of 66% and a specificity of 62% ($p = 0.0009$). The cutoff between controls and recurrent stone formers (0.31) was similar to the value found in the literature (0.33).

## DISCUSSION

Pediatric nephrolithiasis is clearly becoming more prevalent in the United States.[7,8] The exact cause is unclear but proposed etiologies include dietary and physical activity changes and possibly obesity.[8] The associated health care burden is not insignificant.[8,9] As in adults, in children calcium based kidney stones are most common.[7] In addition, children have a high rate of stone recurrence and a metabolic abnormality can often be elicited.[10,11] Thus, we typically perform a standard 24-hour urinary metabolic evaluation after the first stone episode, which includes daily excretion of calcium and citrate, a known inhibitor of calcium crystal growth and aggregation in the urine.

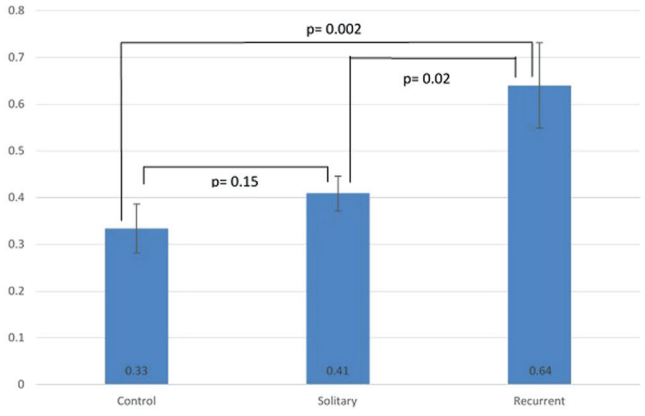


**Figure 1.** Mean calcium-to-citrate ratios by study group

We have previously demonstrated that increased levels of urinary calcium are found in recurrent stone forming children.[4] In a subsequent multivariate analysis increased urinary calcium and low urinary citrate were independent risk factors for stone recurrence.[5] The present study considers the ratio of these indices as an additional bedside tool to identify children who may be at increased risk for relapse. We found that recurrent stone formers had greater mean calcium-to-citrate values than solitary stone formers or normal controls. Less significant differences were seen between controls and solitary stone formers in the overall cohort. It is noteworthy that 41% of those in the control group had values above 0.33.

There are limited data in the literature regarding use of calcium-to-citrate ratios in children. Srivastava et al examined hypercalciuric children with and without kidney stones and calculated calcium-to-citrate ratios based on a single random voided specimen (rather than 24-hour collection).[6] ROC curves and multiple likelihood ratios were used to assess the power of urinary ratios to predict stone risk. In that series a calcium-to-citrate ratio of 0.33 seemed to provide good discrimination between children with hypercalciuria who did and did not form kidney stones. When this cutoff was applied to our data set, it appeared to distinguish between recurrent stone formers (70% with abnormally high values) and normal controls (41%) with statistical significance. When ROC curves were performed on our data set, the cutoff value between recurrent stone formers (with and without hypercalciuria) and controls was 0.31. This value was slightly higher than the optimum cutoff between solitary stone formers and controls (0.28). There does not appear to be a clear reason from a stone physiology standpoint for this small difference.

Sikora et al evaluated multiple crystallization risk factors in children.[12] In 24-hour urine samples they found higher ratios of calcium to citrate as well as calcium to magnesium in recurrent vs solitary stone formers. Similar to our study, they found considerable overlap in individual values and thus concluded that these ratios may have a more supplementary role in the evaluation of children with

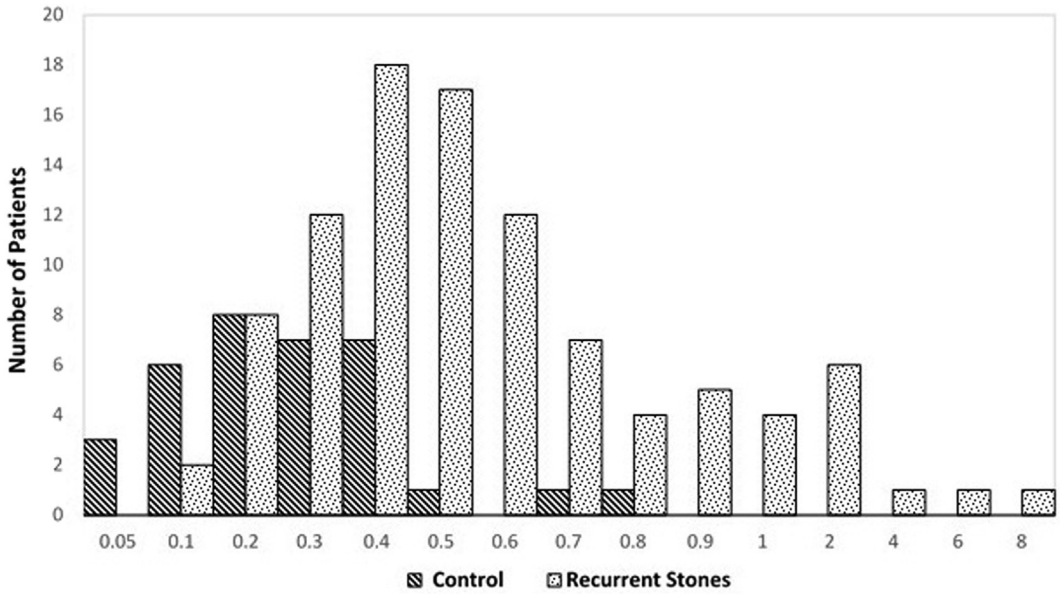


**Figure 2.** Histogram of calcium-to-citrate ratios in recurrent stone formers and normal controls

calcium nephrolithiasis. In a series of adults Höbarth and Hofbauer also reported that calcium-to-citrate ratios were able to discern recurrent from solitary stone formers.[13]

Random calcium-to-citrate levels can be obtained with a voided specimen in the office, making it a simple screening test in the initial evaluation of a patient presenting with nephrolithiasis. However, the precise correlation between random and timed values is currently not well defined. In addition, random calcium values may fluctuate with diet and hydration. It is also unknown whether excretion of calcium and citrate changes in tandem during the course of the day, an issue resolved by the time averaging effect of a 24-hour collection. Studies are needed to assess the usefulness of a random calcium-to-citrate ratio in children. In addition, further analyses may be helpful in assessing whether calcium-to-citrate ratios are more sensitive than calcium-to-creatinine ratio or citrate-to-creatinine ratio in predicting whether a child is at risk for recurrent stones.

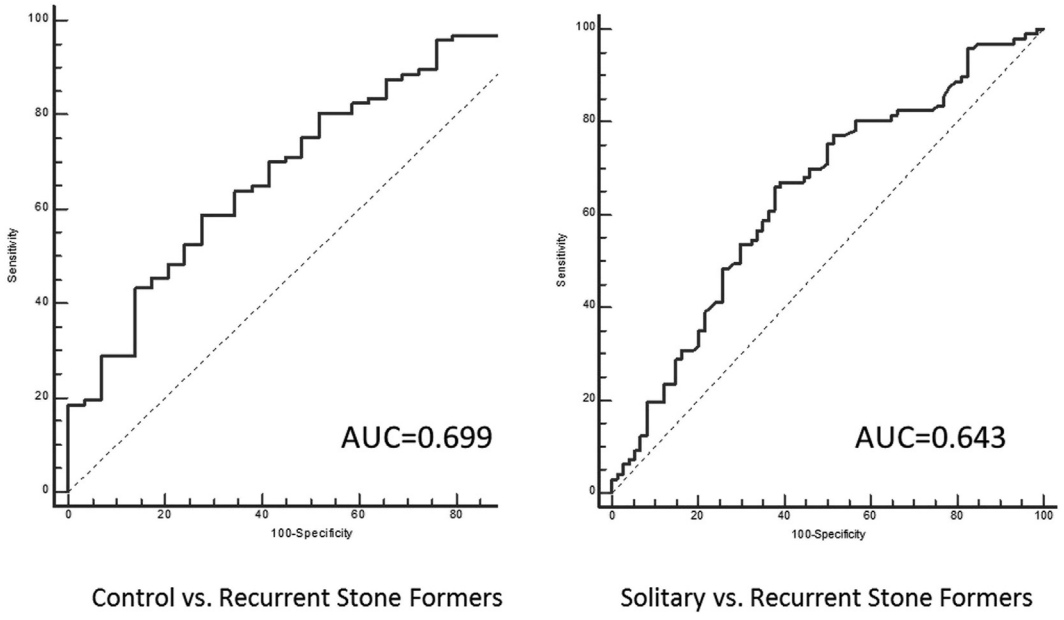


**Figure 3.** ROC curves of controls vs recurrent stone formers and solitary vs recurrent stone formers

Limitations of our study include the retrospective nature of the data collection, which can lead to selection and classification bias. Blinding of the classification to the results of the 24-hour urinary metabolic profiles was done to limit confounding. Other potential limitations include the decision to stratify patients presenting with multiple unilateral or bilateral stones into the recurrent stone forming group while they may have had only 1 symptomatic stone episode. There may be unknown differences between this subpopulation and those children who present with a solitary stone and subsequently experience a relapse. It is also unknown whether those in the solitary stone forming group would ultimately experience a recurrent stone without dietary and/or pharmacotherapeutic intervention. The number of patients in the control group was somewhat small compared to the study groups, which likely reflects the difficulty in obtaining healthy volunteers to perform two 24-hour urine collections.

## CONCLUSIONS

There are significant differences in urine calcium-to-citrate ratios between solitary and recurrent calcium stone forming children. Solitary stone formers tended to have a higher ratio than controls. Further analysis is needed to assess the correlation of a random spot calcium-to-citrate ratio to a value obtained by 24-hour urine collection. Additional analysis may be helpful to assess whether the contribution of high calcium, low citrate or both is associated with risk of recurrence. These results may allow more precise risk stratification of children after the first stone episode.

## REFERENCES


1. Copelovitch L: Urolithiasis in children: medical approach. Pediatr Clin North Am 2012; **59:** 881.
2. Bergsland KJ, Coe FL, White MD et al: Urine risk factors in children with calcium kidney stones and their siblings. Kidney Int 2012; **81:** 1140.
3. DeFoor W, Asplin J, Jackson E et al: Urinary metabolic evaluations in normal and stone forming children. J Urol 2006; **176:** 1793.
4. DeFoor W, Minevich E, Jackson E et al: Urinary metabolic evaluations in solitary and recurrent stone forming children. J Urol 2008; **179:** 2369.
5. DeFoor WR, Jackson E, Minevich E et al: The risk of recurrent urolithiasis in children is dependent on urinary calcium and citrate. Urology 2010; **76:** 242.
6. Srivastava T, Winston MJ, Auron A et al: Urine calcium/citrate ratio in children with hypercalciuric stones. Pediatr Res 2009; **66:** 85.
7. Tasian GE and Copelovitch L: Evaluation and medical management of kidney stones in children. J Urol 2014; **192:** 1329.
8. Hernandez JD, Ellison JS and Lendvay TS: Current trends, evaluation, and management of pediatric nephrolithiasis. JAMA Pediatr 2015; **169:** 964.
9. Kusumi K, Becknell B and Schwaderer A: Trends in pediatric urolithiasis: patient characteristics, associated diagnoses, and financial burden. Pediatr Nephrol 2015; **30:** 805.
10. Battino BS, DeFoor W, Coe F et al: Metabolic evaluation of children with urolithiasis: are adult references for supersaturation appropriate? J Urol 2002; **168:** 2568.
11. Tasian GE, Kabarriti AE, Kalmus A et al: Kidney stone recurrence among children and adolescents. J Urol 2017; **197:** 246.
12. Sikora P, Zajaczkowska M and Hoppe B: Assessment of crystallization risk formulas in pediatric calcium stone-formers. Pediatr Nephrol 2009; **24:** 1997.
13. Höbarth K and Hofbauer J: Value of routine citrate analysis and calcium/citrate ratio in calcium urolithiasis. Eur Urol 1991; **19:** 165.


## EDITORIAL COMMENT

Prognostic factors predicting kidney stone recurrence in the pediatric population are lacking. Management decisions made in pediatric stone formers are often guided by adult data. Children have important differences in urinary risk factors relative to adults.[1]

This retrospective study identifies a potential composite urinary factor that may distinguish children at risk for recurrent stones. We must temper the expectation that the calcium-to-citrate ratio will be the major determinant of recurrent stone risk. Rather the ratio probably represents a potential factor that may be implicated (reference 12 in article). This study population was likely already undergoing interventions that may have altered the natural course of disease. In examining the ROC curves it is noteworthy that the cutoff for the calcium-to-citrate ratio was lower in recurrent stone formers than in single stone formers compared to controls. Prospective studies examining the usefulness of this urinary ratio in pediatric subjects are needed.

**Shamir Tuchman**
*Division of Pediatric Nephrology*
*Children's National Health System*
*Washington, D.C.*

## REFERENCE

1. Tefekli A, Esen T, Ziylan O et al: Metabolic risk factors in pediatric and adult calcium oxalate urinary stone formers: is there any difference? Urol Int 2003; **70:** 273.

## REPLY BY AUTHORS

We agree that more research is needed to solidify the role of the calcium-to-citrate ratio in predicting kidney stone recurrence in children. However, we want to clarify that although patients had received dietary advice, they were not administered pharmacological intervention during the observation period before collection of the 24-hour urine for metabolic profile.