An Update on the Changing Epidemiology and Metabolic Risk Factors in Pediatric Kidney Stone Disease

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Summary
Nephrolithiasis in children is a painful and costly disease that may also have detrimental long-term effects on kidney function. Recent data provide evidence that the incidence of nephrolithiasis in children is rising. Children who are white, female, and adolescent seem to have the highest risk for forming symptomatic kidney stones. Although the reasons for the rising incidence and demographic discrepancies in pediatric nephrolithiasis are not yet clear, recent investigations into urine chemistry provide clues regarding predisposing metabolic risk factors. As more data emerge regarding epidemiologic and metabolic characteristics of pediatric kidney stone formers, we hope to gain a better understanding of the causes of kidney stone disease and, ultimately, provide better strategies for stone prevention in children.

Introduction
Nephrolithiasis is a painful and costly medical condition that begins with solute supersaturation (SS), crystal formation, and aggregation, followed by retention in the collecting system and further growth. In adults, kidney stones are associated with hypertension and chronic kidney disease, as well as an increasing financial burden (1–5). Although relatively rare in the pediatric population, recent data regarding incidence (6), cost (5), and inpatient hospitalization rates (7,8) for children with kidney stones bring into sharp focus the need to gain a better understanding of the metabolic underpinnings as well as environmental contributors to pediatric nephrolithiasis so that we may improve on strategies for prevention.

Like many nephrologic conditions, there is a paucity of data on children compared with adults regarding nephrolithiasis. As a result, children are often evaluated and treated in a similar manner to adults with the same condition. The limited data available regarding pediatric nephrolithiasis suggest that there are, indeed, differences between pediatric and adult stone formers (SFs). This review summarizes the most recent findings regarding the epidemiology and metabolic risk factors associated with so-called idiopathic pediatric nephrolithiasis. I conclude with a brief discussion of potential contributing factors to the increase in pediatric kidney stone disease. Anatomic and genetic abnormalities, as well as other medical conditions that predispose children to nephrolithiasis, are not addressed in this review.

Epidemiology

Incidence
A large study incorporating a nationally representative sample suitable for defining the true incidence of nephrolithiasis in US children has not yet been done. Population-based data appropriate for defining incidence in pediatric patients are limited to studies done outside the United States (9,10) and one study that investigated state-wide data in South Carolina (6). It is unclear whether these data can be extrapolated to the general US pediatric population.

In South Carolina, data from all pediatric emergency department visits in the state with International Classification of Diseases, Ninth Revision codes consistent with nephrolithiasis or urolithiasis was used to estimate incidence (6). The incidence of nephrolithiasis for children aged ≤18 years was found to be 18.5 per 100,000 children in 2007, an increase from 7.9 per 100,000 in 1996. Data from Iceland revealed an incidence of 5.6 per 100,000 children aged 0 to 18 years on the basis of 26 new diagnoses of nephrolithiasis during a 6-year period among a national population of approximately 78,000 children (9). A study from Japan using a questionnaire sent to 1218 hospitals to determine the number of new diagnoses of nephrolithiasis on the basis of either imaging findings or clinical determination by a urologist estimated the incidence of nephrolithiasis to be 17.7 per 100,000 males and 12.4 per 100,000 females aged 10 to 19 years (10).

True incidence data in the US adult population are also rare. A study from a single county in Minnesota used radiologic and clinical data maintained in the Rochester Epidemiology Project diagnostic index to determine an incidence rate of 101.8 per 100,000 adults but is limited by small population size (11). Two studies by Curhan and colleagues (12,13) used large questionnaire-based databases to extrapolate overall incidence rates for male and female adults and found them to be 306 and 95 per 100,000 person-years.
respectively. Although none of these studies truly defines the incidence of nephrolithiasis in the pediatric or adult populations of the United States, we can conclude that adults have a higher risk for developing stone disease than do children. Although pediatric patients are still less likely to be afflicted with kidney stones than adults, the seeming increase in incidence is concerning.

**Gender**

On the basis of data from adult populations, nephrolithiasis affects men more than women (14,15). Pediatric nephrolithiasis, conversely, seems to be more common in girls on the basis of recent data. Interestingly, analysis of National Health and Nutrition Examination Survey (NHANES) data by Stamatelou et al. (15) revealed that the only adult age group in which the prevalence for nephrolithiasis was higher for women compared with men was 20 to 29 years, perhaps foreshadowing more recent data in pediatrics. In South Carolina, the male-to-female ratio is 1:1.4 for all children, and the discrepancy becomes more pronounced as children enter adolescence (Figure 1) (6). In research by Edvardsson et al. (9) among the Icelandic pediatric population, 58% of pediatric SFs were female. Analysis of data regarding children who were hospitalized for nephrolithiasis revealed that girls account for only 46% of all admissions to children’s hospitals but 56% of hospitalizations for kidney stones (7). The authors calculated that female gender imposes a relative risk of 1.5 for hospitalization for nephrolithiasis. In a similar study, Routh et al. (8) revealed comparable data and also found female predominance to be increased in adolescence. In a study that included a review of the literature regarding gender prevalence in pediatric nephrolithiasis, Novak et al. (16) also concluded that girls were more commonly admitted to the hospital for nephrolithiasis, despite finding that only one of 10 previously published case series showed a female predominance of pediatric SFs.

**Race**

Nephrolithiasis more commonly affects non-Hispanic white individuals as compared with non-Hispanic black individuals (15,17). This discrepancy seems to be true in the pediatric population as well (6–8). With regard to the Hispanic population, most studies (both adults and pediatric) have found that Hispanic individuals have a risk for nephrolithiasis that is higher than black individuals but not as high as for white individuals (7,8,14,15). In an intriguing exception, the study by Mente et al. (17) of Canadian SFs found that Latin American individuals had a higher risk for stone formation than white individuals, which may be due to the heterogeneity of Canada’s Hispanic population compared with the US’s mostly Mexican American Hispanic population.

**Age**

The risk for kidney stones increases with age in adults up to a peak risk in the 50s and 60s, although some data reflect the highest risk for women to be in the late 20s and 30s (11,15,18). Extrapolation to pediatrics would predict lower risk with younger ages, and recent data support this. During the 12-year period examined in our study, we found the lowest incidence in children aged 0 to 3 years (0.6 per 100,000) and a consistent increase through adolescence, when the overall incidence for children aged 14 to 18 years was 34.9 per 100,000 (6). Children aged 14 to 18 years had a 10.2-times greater risk for nephrolithiasis compared with children aged 0 to 13 years. Risk for hospitalization for nephrolithiasis follows the same pattern, with the highest risk in adolescents and a decreasing trend to the lowest risk among infants (7). Older children are also more likely to have ureteral stones, whereas younger children more commonly have renal stones (19,20). Regarding spontaneous passage of stones, age typically is not a predictive factor, but stone size, regardless of age, can predict likelihood of spontaneous passage, with stones >5 mm less likely to pass versus stones <5 mm (19,20).

**Other Considerations**

Presenting signs and symptoms of nephrolithiasis in the pediatric population are fairly heterogeneous. Pain is a more common presenting symptom in older children and is present in 47% to 80% of children with nephrolithiasis (21–24). Thirty-two percent to 55% of children with nephrolithiasis present with gross hematuria (21,23). In a study from their experience in a single emergency department, Persaud et al. (24) found that the strongest predictors for finding kidney stones on unenhanced computed tomography scans were history of previous stones, history of vomiting, and blood on urinalysis performed during the emergency department visit. They found no correlation between risk for kidney stones and history of hematuria or positive family history for stones. A history of fever strongly predicted no nephrolithiasis on computed tomography.

With regard to geographic distribution of nephrolithiasis, adults living in the southeastern United States have the highest prevalence of kidney stone disease (25), but no such study has been performed of children. There are no data from the United States regarding risk for kidney stone disease, and it is possible that the incidence of stone disease is higher among children in the southeastern United States (25). Much of this information is derived from Southern patients, who have been shown to have a higher prevalence of stone disease than other regions in the United States (25). Where this may occur, the incidence varies by geographic region, with children in the southeastern United States, the Southeastern United States, and the South-Eastern United States being reported as the regions with the highest incidence of nephrolithiasis (25). The highest incidence was found among children living in the southeastern United States, with an incidence of 34.9 per 100,000 (6). Children aged 14 to 18 years had a 10.2-times greater risk for nephrolithiasis compared with children aged 0 to 13 years. Risk for hospitalization for nephrolithiasis follows the same pattern, with the highest risk among patients aged 14 to 18 years. Older children are also more likely to have ureteral stones, whereas younger children more commonly have renal stones (19,20). Regarding spontaneous passage of stones, age typically is not a predictive factor, but stone size, regardless of age, can predict likelihood of spontaneous passage, with stones >5 mm less likely to pass versus stones <5 mm (19,20).

**Figure 1. | Incidence of pediatric nephrolithiasis in South Carolina.**

In 2007, the incidence of nephrolithiasis for girls was 21.9 versus 15.3 for boys, which reflects a change from the similar incidence (7.7 versus 8.0) observed in 1996. Incidence is expressed as number of unique cases of nephrolithiasis per 100,000 children from each specific demographic (6).
stones in rural versus urban adult populations, although our own pediatric data revealed a higher incidence of kidney stones in children living in rural communities (6).

**Metabolic Factors**

The literature varies widely with regard to the percentage of pediatric patients who have nephrolithiasis and an identifiable underlying metabolic risk factor, ranging from 33% to 93% (19,20,22,23,26–29). Despite the variation in percentage of metabolic risk factors among pediatric SFs, it is clear that, in general, younger patients are more likely to have an identifiable metabolic risk factor. Underlying metabolic risk factors generally refer to innate characteristics of one's physiology that are stable over time and result in urinary conditions that are more conducive to stone formation. Underlying metabolic abnormalities can include enteric/absorptive, endocrinologic, or renal sources. “Identifiable” risk factors are limited by (1) whether we know they exist, (2) how they are defined, and (3) whether we can or do test for them. Of note, although not “metabolic,” anatomic abnormalities that result in urinary stasis or turbulent flow should also be considered when evaluating a child's underlying risk factors for stone formation.

Stone formation is a multifactorial process that involves both the patient's underlying metabolic background and environmental conditions that promote nephrolithiasis, such as volume depletion, infection, or intake of foods high in lithogenic solutes. Some underlying metabolic derangements, such as those found in children with Dent disease, primary hyperoxaluria, or Lesch-Nyhan syndrome, are severe enough that they can result in kidney stone formation without help from environmental stimuli. It is likely that more often our pediatric SFs have a milder underlying metabolic risk factor that lowers the threshold for forming a stone but still requires some contribution from the modifiable environment. Children with underlying metabolic characteristics that put them closer to that threshold will form stones more readily from smaller environmental contributions than children with a better metabolic profile, in whom the same environmental conditions will not lead to stone formation. A primary goal for research in pediatric nephrolithiasis will be to explore identifiable risk factors further and determine which ones are amenable to change.

Pediatric SFs predominantly form calcium-based calculi (30). Studies show that calcium is present in 72% to 88% of pediatric kidney stones (20,22). The same studies show uric acid present in only 2% to 3% of stones in pediatric patients, whereas uric acid is present in 11% of kidney stones in adults (31). Although struvite (ammonium magnesium phosphate) stones previously accounted for a more significant proportion of pediatric stones (17% in one study), improvements in the diagnosis and treatment of urinary tract infections have made this type of stone rare (20,22).

Why do younger patients form more calcium-based stones and fewer uric acid stones? Part of the answer may be that pediatric patients generally have a slightly higher urinary pH than adults. In a comparison between pediatric and adult 24-hour urine samples, Defoor et al. (32) showed that the mean urinary pH for children was 6.44 versus 6.05 for adults ($P < 0.001$). Another study of pediatric patients also showed an indirect relationship between pH and age (33). Because uric acid stones form preferentially in acidic urine, this difference in urinary pH may protect children from uric acid stones, despite that children have higher excretion of uric acid when adjusted for creatinine excretion (32–34).

**Promoters of Stone Formation**

The key determinant of calcium stone formation is urinary SS of calcium oxalate (SS CaOx) and calcium phosphate (SS CaP). SS generally describes the likelihood of crystals forming in solution and reflects the ratio of a salt's concentration in urine to its solubility. If SS is $>1$, then crystals will form; at SS $<1$, crystals will dissolve. Low urine volume generally increases solute concentration and, therefore, SS and further contributes to stone formation by leading to urinary stasis. The SS CaOx is primarily determined by the concentrations of calcium and oxalate in the urine, whereas SS CaP is primarily determined by urinary calcium concentration and urinary pH; both SS CaOx and SS CaP are affected inversely by citrate concentration (35). Children have higher urinary calcium excretion than adults when adjusted for creatinine excretion or body weight (32,36–38). Studies also show that children have higher urinary SS CaP than adults (32) and that stone-forming children have higher SS CaOx than non–stone-forming children (39,40). In addition, recurrent pediatric SFs have higher calcium excretion when adjusted for creatinine excretion or body weight than solitary pediatric SFs, but this did not translate into significantly different SSs (40,41).

Elevated urinary oxalate augments SS CaOx and contributes to formation of calculi (31,42). Sources of oxalate include diet, the liver, erythrocytes, and metabolism of ascorbate. While data are mounting regarding oxalate, there remains much to learn regarding absorption, distribution, metabolism, and ultimate fate of oxalate in humans. Urinary oxalate excretion (adjusted for creatinine excretion) is considerably higher in children than in adults (32). Hyperoxaluria is present in approximately 14% to 18% of adult SFs (31,43) and approximately 11% to 20% of pediatric SFs (22,23,44). However, a study by Defoor et al. (39) did not find a significant difference in urinary oxalate excretion between SFs and non-SFs when adjusted for creatinine excretion. Oxalate excretion was not found to be as important as calcium regarding risk for recurrent kidney stones in children in one study (37). Taken together, the degree to which urinary oxalate contributes to pediatric nephrolithiasis is not clear.

Although a detailed discussion of the known genetic forms of primary hyperoxaluria is beyond the scope of this article, it is worth mentioning that milder forms may be more prevalent than initially believed and comprehensive diagnostic workup should be considered in children with nephrolithiasis and significant hyperoxaluria. If urine oxalate is found to be elevated, then initial screening should include analysis of urine for glycolate, glycerate, and glyoxalate at a reputable laboratory. Additional testing that may be indicated depending on the clinical situation and results of other tests are plasma oxalate, liver biopsy, and/or genetic testing.

No discussion of nephrolithiasis is complete without mention of Randall plaque. Randall plaque is composed of
CaP and initially forms at the basement membrane of the thin loops of Henle before expanding to the interstitium (45). Formation of Randall plaque has been established as an integral part of idiopathic CaOx stone disease. Unfortunately, this is an area of glaring deficiency in the pediatric literature. It is unclear at what age Randall plaque begins to form. To date, there is no published evidence that Randall plaque forms in children, but that may be simply because no one has looked.

Uric acid stones are uncommon in the pediatric population despite that children naturally have a higher urinary excretion of uric acid when adjusted for creatinine excretion (32). Although hyperuricosuria may be a risk factor for calcium stone formation (46), one study concluded that excessive urinary uric acid excretion is not likely to increase the risk for calculi in the pediatric population (47). Another common lithogenic factor is low urinary volume, found in the majority of idiopathic SFs (48). Urine pH plays a role in stone risk as well. Low urine pH is the major determinant of risk for uric acid stones, whereas high pH is associated with CaP stones. Last, urinary tract infection used to play a significant role in pediatric nephrolithiasis as the major cause of ammonium magnesium phosphate (struvite) stones. This role has diminished with improved diagnosis and treatment of urinary tract infections, although the practitioner should always remember that an infected kidney stone is a true urologic emergency.

Inhibitors of Stone Formation

Citrate is a substance that is found in urine and chelates calcium, making it unavailable for binding with oxalate and phosphate and thereby lowering urinary SS and preventing stone formation (49,50). Urinary citrate levels are highest in young children and decrease into adulthood (32,33), but relative hypocitraturia is a common finding in pediatric nephrolithiasis (22,23,28,39,40,51,52). Hypocitraturia has also been shown to be a risk factor for recurrent stone disease in children (37,41). Treatment with oral citrate supplementation has been shown to reduce stone risk (53,54).

Although citrate is the best described inhibitor of stone formation, magnesium is also included in the discussion of kidney stone prevention. Although not as exhaustively researched as hypocitraturia, hypomagnesuria has been established as a risk factor for formation of calculi (55,56). In children, urinary magnesium excretion decreases with age when adjusted for creatinine excretion or body weight (33). A group from Turkey found that hypomagnesuria was more commonly associated with nephrolithiasis in children than in adults (57). Stone-forming children have a higher urinary calcium-to-magnesium ratio than non-stone-forming children, and children with recurrent stones have a higher calcium-to-magnesium ratio than solitary SFs (40). Treatment with oral magnesium alone has not been shown to improve stone risk, although risk improves when combined with citrate supplementation (58,59).

Other endogenous inhibitors of stone formation have been identified, including glycosaminoglycans (60), Tamm-Horsfall protein (61), pyrophosphate (62), nephrocalcin (63), and osteopontin (64), among others. The mechanism by which they reduce kidney stone burden is through bonding with crystal surface calcium, thereby getting in the way of crystal aggregation. Although there is a paucity of definitive data regarding these inhibitors in pediatric nephrolithiasis, they serve as an intriguing and potentially fertile area for further investigation.

Why the Increasing Incidence in Pediatric Nephrolithiasis?

From what we have reviewed so far, it is clear that the incidence of pediatric nephrolithiasis is increasing, but no reason for the increase has been elucidated. Although there is a lack of clear data, there is plenty of speculation. Some of the most oft-discussed potential causes for the increase in pediatric kidney stone disease are obesity; changes in dietary habits such as increased sodium intake, decreased calcium intake, decreased water intake, and increased fructose intake; and increasing use of antibiotics. The merits of each possibility are briefly discussed.

Obesity as a cause for the rise in pediatric nephrolithiasis is a very attractive prospect given both the gravity of the obesity epidemic and its apparent temporal relationship to the increase in incidence of kidney stones. However, epidemiologic data cast doubt on this relationship. Between 1999 and 2008, a period in which we observed a significant increase in pediatric kidney stone disease, there was no significant change in the rates of overweight (body mass index [BMI] ≥85th percentile for age) or obesity (BMI ≥95th percentile for age) in US children (65). This holds true when the pediatric population is broken down by gender and specific age groups. The only increase found in analysis of these data was a statistically significant linear trend for 6- to 19-year-old boys for BMI ≥97th percentile.

The putative mechanism by which obesity leads to increased uric acid stone risk is a combination of increased lithogenic solute concentration and decreased urinary pH as BMI increases, thereby predisposing to uric acid crystallization. Although lower urinary pH increases uric acid crystallization, it does not directly affect CaOx crystallization. However, increasing uric acid crystallization may promote heterogeneous nucleation of CaOx, possibly leading to increased risk for CaOx stones in obese individuals (66). A number of studies have shown that overweight and obese adults may be at higher risk for kidney stones and have urine chemistry predisposing to the formation of calculi (66–70), whereas other studies have not shown as clear a link (71–74).

Studies examining the relationship between stone risk and obesity in children are few. Sarica et al. (75) studied 94 children in Turkey and found that overweight children had higher excretion of urinary oxalate and uric acid, higher SS CaOx, lower urine volume, and lower excretion of citrate and magnesium. Although this generally supports the lithogenic effect of higher BMI, some weaknesses in this study should be noted. First, the urinary analytes were corrected using body weight, which does not necessarily equate to excretion rate adjusted using creatinine. This is perhaps best illustrated by the difference in relative excretion of calcium between the two groups. When adjusted for body weight, the overweight group had a higher calcium excretion rate, suggesting increased risk for stones. However, when adjusted for creatinine excretion, the over-
weight group had a lower calcium excretion rate. This example highlights the difficulty in assessing stone risk in populations with highly variable metabolic backgrounds such as children. Rather than using cutoff points to define obesity, hypercalciuria, hyperoxaluria, and other analytes because the patients had variable body weights and creatinine excretion rates, it would have been more illustrative to provide the data as continuous variables. It should also be noted that the definitions they used to define normal, overweight, and obese do not match the definitions used in the United States, and it is unclear whether data from the Turkish pediatric population can be extrapolated to the US population.

Kieran et al. (76) analyzed the relationship between BMI and stone formation in a pediatric population. Their data revealed that 41% of their SFs were overweight or obese, which is slightly higher than the overweight/obesity rate observed in the general pediatric population in their state (77). Interestingly, they found that low body weight was associated with increased severity of stone disease. Eisner et al. (78) analyzed 24-hour urine data from their stone-formation pediatric population and correlated the results to BMI quartiles on the basis of child height and weight as reported by their parents. They found that higher BMI correlated with higher SS CaP but lower urinary oxalate excretion (adjusted for creatinine excretion). Of note, they also found that higher BMI did not correlate with lower urine pH as it does in adults. In our own pediatric stone-formation population, we are finding a slightly lower BMI percentile compared with our general, non-stone-forming pediatric population (unpublished data). When trying to establish a link between obesity and increased stone risk for children, the limited data available are not convincing but certainly warrant continued investigation.

Increased sodium intake may be the most likely culprit leading to the increase in pediatric nephrolithiasis. There is evidence that American children eat too much salt, although NHANES data reflect that salt intake may be declining slightly in the adolescent population (79). Given that most children get a significant portion of their nutrition from school-prepared meals, it is troublesome that 92% of school meals exceed the acceptable upper limit of sodium (80). The strong evidence, both epidemiologic (81,82) and mechanistic (83–86), linking increased sodium intake with increased risk for nephrolithiasis make this area an extraordinarily high priority for research.

Calcium intake has decreased in children in recent years; this may be due, at least in part, to the replacement of milk with sugary drinks (79,80,87,88). There is ample evidence, although counterintuitive, that decreased calcium intake is associated with increased severity of stone disease. Eisner et al. (78) found that higher BMI did not correlate with lower urinary calcium excretion, SS CaOx and CaP, and decreased urinary citrate and continuing to look for other urinary stone promoters and inhibitors. The pediatric population most affected by the increase in stone disease seems to be adolescents and girls, who are more likely to get kidney stones and require hospitalization for treatment. Examination of differences in urine chemistry between boys and girls has not yet been performed and may provide interesting and useful results. Last but perhaps most important, we must continue to investigate potential environmental and dietary factors that could be contributing to the increasing incidence of pediatric nephrolithiasis so that we may better prevent this painful and costly condition.

Disclosures
None.

References