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The increasing pediatric stone disease problem

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***Abstract*:** While once thought to be relatively rare in developed nations, the prevalence of pediatric urolithiasis appears to be increasing, and a number of factors may be contributing to this increase. Many theories are plausible and such theories include the increasing childhood obesity epidemic, a changing sex predilection, climate change, alterations in dietary habits and improving diagnostic modalities. Yet, unlike adult patients, rigorous epidemiologic studies do not exist in pediatric populations. Thus, in the setting of an increasing prevalence of childhood stone disease, improved research is critical to the development of uniform strategies for pediatric urolithiasis management.

***Keywords*:** urolithiasis, pediatric, kidney calculi, epidemiology

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Introduction

While considered to be exceedingly rare in the pediatric patient, a growing body of evidence suggests that urolithiasis is becoming more commonplace in children. In fact, recent publications in the United States lay literature have brought considerable attention to the notion that pediatric stone disease is rising [Worth, 2009; Tarkan, 2008]. Whether such assumptions are valid, they remain largely unproven from an epidemiologic perspective. Most likely, a host of factors are contributing to the changing epidemiology of pediatric urolithiasis, yet unlike in adult patients, the epidemiologic trends occurring in pediatric stone disease have not been studied rigorously. However, with such light cast upon this issue, it is critical for urologists to strive for a better understanding of pediatric urolithiasis. In this review, we hope to identify the poignant factors potentially contributing to an increase in the childhood prevalence of urolithiasis. We further hope to address the shortcomings of the available literature on this topic. Consistently, throughout this manuscript, we have attempted to primarily utilize data from studies performed in pediatric patients only. However, to substantiate many of our proposed theories, we have been forced to extrapolate data from adult studies when necessary.

Pediatric urolithiasis

In adult patients, the lifetime prevalence of developing urolithiasis ranges between 10% and 15% [Stamatelou *et al.* 2003; Coe *et al.* 1992]. The prevalence of stone disease in children, while likely under investigated, is much rarer. From historical reports, 2–3% of children will develop a urinary calculus [Malek and Kelalis, 1975]. However, such prevalence estimates can vary widely and are often dependent upon the geographic location of the reporting center. In countries such as Turkey and Pakistan, regions in which pediatric stone disease is endemic, childhood stone prevalence approaches 15%. Yet, these estimates are tempered by the fact that many calculi found in children born in developing countries are located within the urinary bladder [Rizvi *et al.* 2003, 2002]. A recent report from Pakistan, however, demonstrated a shift in the predominant location of urinary calculi from the bladder to the upper urinary tract over a 13-year period from 1987 to 2000 [Rizvi *et al.* 2002]. Nonetheless, in nations where stone disease is endemic, urolithiasis remains a serious problem accounting for 4–8% of cases of end-stage renal disease during childhood [Sirin *et al.* 1995]. Developing countries provide a great avenue to better understand how changes in pediatric stone disease occur. Particularly as other countries around the world become more westernized in their occupational, social, and dietary habits, we may learn more about how diet affects lithogenesis. Unfortunately, to date, no well-conducted epidemiologic studies have yet been published by authors in parts of the world with endemic stone disease.

The age at which children with urolithiasis initially present is variable and generally ranges between 5 and 15 years of age in most series. It has been suggested that initial stone presentation in children is accompanied by classic symptoms such as flank or abdominal pain in only 50% of cases [Kroovand, 1997]. Yet, in more recent series, approximately 70–80% of children will present symptomatically with either flank pain or abdominal pain, 10–32% will also have gross hematuria, and 4–20% will have a concomitant urinary tract infection (UTI). The majority of pediatric patients will present with stones in an idiopathic manner, but 9–24% will have an associated secondary cause such as congenital urinary tract anomaly, metabolic deficiency, or neurologic disease [Alpay *et al.* 2009; Kalorin *et al.* 2009; Dursun *et al.* 2008; Kit *et al.* 2008; VanDervoort *et al.* 2007; Sternberg *et al.* 2005; Alon *et al.* 2004]. Overall, approximately 50–60% of patients have stones located in the kidney at the time of diagnosis [Passerotti *et al.* 2009; Palmer *et al.* 2005; Sternberg *et al.* 2005; Kroovand, 1997]. With increasing age, though, this ratio is reversed, and in older children, the majority of stones can be found within the ureter [Kalorin *et al.* 2009; Pietrow *et al.* 2002]. Multiple single institution series have reported the predominate stone composition to be either calcium oxalate or calcium phosphate [Kalorin *et al.* 2009; Kit *et al.* 2008; Sternberg *et al.* 2005]. Unfortunately, in most of these series, only 40–60% of stones were available for analysis, limiting the ability to confirm the predominate composition. In the future, more comprehensive stone analysis should be reported.

Evolving epidemiology

In Western countries, in particular, an emerging body of literature suggests that the prevalence of urolithiasis in children is indeed growing [Bush *et al.* 2010; VanDervoort *et al.* 2007]. In historic reports, urinary stone disease has comprised 1 out of every 1000 to 1 out of 7600 pediatric inpatient admissions [Walther *et al.* 1980]. Bush and colleagues challenged this somewhat variable figure in a recent analysis utilizing the Pediatric Health Information System (PHIS), an administrative database currently encompassing millions of inpatient admissions to over 40 free-standing US children's hospitals. Over a 5-year period from 2002 to 2007, the authors found urinary stone disease accounted for 1 out of every 685 admissions (prevalence ratio of 2.4 per 100,000 children) [Bush *et al.* 2010]. Similarly, several single institution series have independently observed a nearly fivefold increase in pediatric patients presenting with urinary calculi over the last decade [Alpay *et al.* 2009; VanDervoort *et al.* 2007].

Epidemiologic trends can be difficult to discern from single-institution series because many factors may have an impact on the pattern of patient referral to one particular hospital or practice. A review from Japan spanning the years 1965 to 2005 found evidence of an increased annual incidence of urolithiasis. In that report, the authors noted an increase in urolithiasis among all ages, including children. However, the most pronounced increase among children occurred between the ages of 10 and 19 [Yasui *et al.* 2008]. Routh and colleagues also used the PHIS database to evaluate trends in pediatric urolithiasis diagnosis [Routh *et al.* 2010a]. Raw data examining the proportion of pediatric patients diagnosed with urolithiasis demonstrated a clear increase over a 10-year period. In 1999, the authors found the rate of urolithiasis diagnosis to be 18.4 per 100,000 patients admitted as compared with a rate of 57 per 100,000 in 2008. After accounting for variability in hospital volume over time, the rate of change in pediatric urolithiasis diagnosis was less dramatic, yet a significant 10.6% annual increase in pediatric urolithiasis diagnosis was still observed. It should be noted that the total number of hospitals included in the PHIS database changed rapidly over the study period from 9 hospitals in 1999 to 42 hospitals in 2008. Data from these studies provide credence to the perception of an increasing pediatric stone prevalence, particularly in North America. Yet, in order to definitively demonstrate the true epidemiologic trend of pediatric stone disease, larger-scale epidemiologic studies will certainly be needed. Furthermore, clear and evident reasons for the perception of rapidly changing estimates of pediatric urolithiasis presently remain uncertain, but several key factors can be suspected.

Proposed theories

As stated previously, one common factor is unlikely to be responsible for epidemiologic trends occurring in pediatric stone disease. More likely, several interrelated factors are combining to increase both the perception and the reality of urolithiasis in children. In the forthcoming sections, we attempt to address the literature supporting some of the prevailing theories affecting pediatric stone disease epidemiology. Many of the hypotheses proposed in the following section will derive their basis from nutritional studies performed by the United States Government, in particular the National Health and Nutrition Examination Survey (NHANES). NHANES first began in the 1960s and remains a major program directed by the National Center for Health Statistics (NCHS) under the purview of the Centers for Disease Control. The data derived from NHANES exists as a series of surveys that address health and nutrition in children and adults over time [NCHS, 2007].

Body habitus

One culprit commonly targeted for the escalation of pediatric urolithiasis is the obesity epidemic that has been sweeping North America for several decades [Ball and McCargar, 2003; Ogden *et al.* 2002]. Evidence from NHANES has demonstrated a tripling of the obesity prevalence amongst US children since the 1980s [Ogden *et al.* 2002]. Subsequent data indicate that the pediatric obesity epidemic may have stabilized over the last several years, but the fact remains that the number of overweight and obese children continues to be high. Among US children aged 2–19, an estimated 17% are considered overweight (body mass index [BMI] ≥95th percentile), and 32% are at risk for being overweight (BMI ≥85th percentile) [Ogden *et al.* 2010, 2006]. The adult literature has drawn a clear correlation between the increase in body mass to overweight and obese levels and the change in urinary excretion of risk factors for calcium-based calculi. Siener and colleagues studied 24-hour urine samples in adult patients and observed a significant positive correlation between increasing BMI and increasing urinary sodium and uric acid excretion. An inverse relationship between BMI and urine pH was also observed [Siener *et al.* 2004]. In other studies of adult stone formers, a relationship between increasing BMI, lower urine pH, and increased urinary solute excretion has been observed [Taylor and Curhan, 2006].

Yet, the link between childhood obesity and urolithiasis is more tenuous as few studies have directly addressed this issue in children. In select series, however, up to 30% of pediatric stone formers have body weights greater than the 90th percentile for age [VanDervoort *et al.* 2007]. A study published in 2008 compared the 24-hour urine studies of 44 obese children with similar studies in 50 normal weight controls. Although the results were not stratified according to increasing BMI, in general, the investigators found higher rates of hyperoxaluria, hyperuricosuria, hypercalciuria and hypocitraturia in obese children [Sarica *et al.* 2008]. Eisner and colleagues recently reviewed urinary parameters in children and did stratify them by World Health Organization criteria for BMI (BMI <25, normal; BMI 25–30, overweight; and BMI >30, obese). Interestingly, as BMI increased, the excretion of urinary oxalate decreased while the supersaturation of calcium phosphate increased. Key urinary parameters such as the excretion of urinary calcium and citrate as well as urine pH remained unchanged [Eisner *et al.* 2009]. A recent study examined the role of body fat percentage and glucocorticoid levels in children as a corollary to changes in urinary parameters, and with increasing body fat and urinary free cortisol, the excretion of uric acid and oxalate appeared to increase. Urinary calcium, on the other hand, appeared to be more closely related to dietary intake of sodium and protein [Shi *et al.* 2010].

In contrast, some authors have failed to demonstrate a link between pediatric obesity and urolithiasis. Kieran and colleagues collected obesity related data from 134 children managed for symptomatic renal and ureteral calculi [Kieran *et al.* 2010]. When the authors stratified children according to BMI criteria set forth by the US Centers for Disease Control, they were unable to identify any significant differences in stone characteristics by body mass. Furthermore, in 59% of the patients presenting with symptomatic calculi, body weight was considered normal or low for age. The conflicting and preliminary nature of these studies underscore our primitive understanding of how body mass might affect urinary stone risk in children. Decidedly, the strong connection between body mass and urolithiasis demonstrated in adult patients has yet to be accomplished in children. In the authors' view, the majority of pediatric patients with urolithiasis are indeed not obese. Thus, attaining a better understanding of how current dietary intake is changing among children with urolithiasis may be of greater importance.

Fluid status

Fluid intake and overall hydration are thought to be two of the most important and real risk factors for both *de novo* stone development as well as stone recurrence. Borghi and colleagues in a 5-year prospective study showed that increased fluid consumption in adults with idiopathic calcium-based stones results in a statistically significant decrease in stone recurrence as well as a longer time to recurrence [Borghi *et al.* 1996]. Presumably, alterations in the types and volumes of fluids children are consuming may be influencing patterns of stone development. In the following sections, we consider the available literature describing changes in childhood fluid intake and environmental factors affecting body hydration.

Beverage consumption. The beverages children consume as a source of energy appears to be evolving. A food survey conducted by the US government between 1977 and 2001 demonstrated such changes [Nielsen and Popkin, 2004]. During the study period, the daily consumption of milk among children aged 2–18 years decreased by nearly 50% and sugar sweetened soft drink consumption increased by a similar factor. Similarly, French and colleagues compared soft drink consumption in the mid-1970s with that of the mid-1990s. The authors found a 48% increase in the prevalence of soft drink consumption and a near doubling of daily volume consumption [French *et al.* 2003]. However, the changes in beverage consumption appear to have been changing over a longer period of time. Popkin recently reported that the availability of milk for human consumption reached its peak in the United States following World War II in the 1940s, and since that time, milk availability has been steadily declining [Popkin, 2010].

However, what literature is available to correlate urolithiasis and beverage consumption? In attempting to answer this question, few quality studies can be found, none of which have been performed in children with stones. One previous publication in the adult literature did find a link between sugar sweetened soft drink beverages and urolithiasis. Shuster and colleagues suggested that a higher rate of stone recurrence exists in patients that consume sweetened soda as compared with those abstaining from such beverages [Shuster *et al.* 1992]. On the other hand, two large-scale epidemiologic studies in adults arrived at a different conclusion. A prospective study by Curhan and colleagues used longitudinal data of over 45,000 men in the US Government funded Health Professionals Followup Study to study the association of beverage consumption and stone formation in adults. These authors found that consumption of 240 ml of caffeinated coffee and tea reduced stone formation by 10–15%. While the initial analysis demonstrated an association between sweetened soda consumption and stone risk, that association was lost after controlling for additional lithogenic risk factors. Interestingly, the relative risk of forming a stone increased by 35% in those consuming at least 240 ml of apple juice daily [Curhan *et al.* 1996]. A second study by Curhan and colleagues used the Nurses' Health Study to evaluate beverage consumption and stone risk in adult women. Again coffee and tea consumption led to inverse risk for stone formation while grapefruit juice increased stone risk by 44% [Curhan *et al.* 1998].

Environmental changes. A changing climate may also contribute to an increase in the number of children with urinary stones. Even radical short-term climate change can have an impact on the urinary milieu leading to lithogenesis. Data from United States military personnel stationed in arid climates report a mean time to stone formation of 90 days following deployment [Evans and Costabile, 2005]. In the same vein, areas such as the Southern United States have been termed 'stone belts' due to the higher average temperatures in these regions. Patients living in these 'stone belts' are thus prone to stone formation at higher rates presumably due to higher mean annual temperature and resultant dehydration. Climate change due to cyclical weather trends or due to global warming may be impacting the expanse of the 'stone belt' in the US. A recent study used mathematical modeling to suggest that an expansion of areas at high risk for stone formation is likely to occur as mean annual temperatures increase in the United States [Brikowski *et al.* 2008]. Brikowski and colleagues predicted that the percentage of US residents living within a region at high risk for stone disease will grow from 40% currently to 56% by 2050 and 70% by 2095 [Brikowski *et al.* 2008]. Further analysis of the data set used by Brikowski and colleagues was performed and reported by Fakheri and Goldfarb in a letter to the editor published in *Kidney International* [Fakheri and Goldfarb, 2009]. Here, the authors purported that much of the association between increases in ambient temperature and stone formation reported by Brikowski and colleagues may be most evident in males due to their greater occupational exposure to environmental temperatures. The authors also positively correlated stone risk and rising temperature [Fakheri and Goldfarb, 2009]. Certainly, investigators from arid climates across the globe have reported a seasonal variation in stone prevalence which coincides with increased annual temperature [al-Hadramy, 1997].

The exact manner in which the results of the aforementioned studies can be applied to children is unclear since no studies have directly evaluated beverage consumption, fluid status, and climate in pediatric stone formers. However, a few plausible theories can be suggested. First, climate changes, whether due to seasonal cycles or due to real global warming trends, may be leading to a state of relative dehydration in children. Such variation when combined with decreasing water consumption and increasing sugar sweetened beverage consumption may be affecting urinary stone risk. Second, declining milk consumption may be altering calcium and oxalate metabolism. Because enteral calcium complexes with intestinal oxalate preventing absorption, oxalate absorption is inversely related to oral calcium intake. Perhaps the decreasing consumption of milk products by children is contributing to an increase in urolithiasis due to an increase in urinary oxalate. Evidence of this theory is present in a randomized study comparing a low calcium diet to a normal calcium diet in adults with idiopathic hypercalciuria. Adults adhering to a low calcium diet demonstrated decreases in urine calcium and increases in urinary oxalate [Borghi *et al.* 2002]. Future studies should examine the role of beverage consumption in children with urolithiasis.

Dietary intake

American adults and children alike consistently consume more sodium in their daily diet than is recommended. A recent report from the US government showed that more than 80% of adults consume more than the recommended daily 2300 milligram limit of sodium [Gunn *et al.* 2010]. Furthermore, the US Institute of Medicine estimates that dietary sodium intake in children aged 6–11 has increased from an average of 2000 mg per day in the 1970s to more than 3000 mg per day in the early 2000s [US Institute of Medicine, 2010].

The proximal tubule of the kidney handles sodium and calcium excretion in parallel. As sodium intake increases, the net urinary excretion of calcium mirrors that of sodium [Breslau *et al.* 1982]. Daily dietary intake of sodium has previously been identified as an important modifiable risk factor for stone recurrence in adult patients with calcium-based stones. Patients adhering to diets that limit sodium have been shown to reduce both hypercalciuria [Nouvenne *et al.* 2010] and stone formation [Taylor *et al.* 2009; Borghi *et al.* 2002]. Presumably, by modulating daily sodium intake, calcium excretion can be reduced thus lowering the risk of calcium-based stone development. Because 90% of the excess sodium US adults consume is believed to come from processed foods and restaurant foods, not from table salt [Gunn *et al.* 2010], the sources of dietary sodium cannot be overlooked. Additional epidemiologic studies, in European and North American adults suggest 75% of sodium intake is derived from consumption of processed foods [Brown *et al.* 2009]. Such data in children are harder to come by. But the few available studies suggest that the predominant source of sodium in the diet of children mirrors that of adults [Brown *et al.* 2009]. Bearing these data in mind, we must strive to better understand how sodium intake correlates with nephrolithiasis in the pediatric population.

Food additives in the diet may have an influence on pediatric stone disease as evidenced in the 2008 Chinese outbreak of melamine contamination. Used surreptitiously as a food additive to falsely increase protein content on food labels, melamine was added to infant formula by Chinese manufacturers. Following the discovery of renal toxicity in animals [Brown *et al.* 2007], an apparent, albeit tenuous, link between melamine, nephrotoxicity and urinary stones was established [Zhang *et al.* 2009]. Subsequently, a host of information regarding these associations came from government-sponsored screening programs instituted throughout China. The incidence of urolithiasis in infants exposed to melamine ranges from 1% to 8.5% depending upon the screening center [Guan *et al.* 2009; Zhang *et al.* 2009; Zhu *et al.* 2009]. Almost universally, melamine-associated urolithiases were small in size (<0.5 mm) and had a sand-like quality. In addition, many affected patients were asymptomatic at diagnosis and were identified based upon screening sonograms. Most series have found a strong positive correlation between urolithiasis incidence and exposure to formula containing high levels of melamine (>500 parts per million of melamine) [Guan *et al.* 2009; Zhu *et al.* 2009]. Fortunately, a conservative regimen of intravenous hydration and urinary alkalinization has proved successful for the resolution of stones in the majority of affected patients. Thus, the melamine exposure epidemic serves as a reminder of the importance of diet in the process of lithogenesis.

Therapeutic diets

In a small subset of children with epilepsy, resurgent use of the ketogenic diet may lead to new stone formation. The ketogenic diet, a diet composed of high-fat and low-carbohydrate intake, has been used effectively to control severe epilepsy [Bergqvist *et al.* 2008]. In recent years, the popularity of the ketogenic diet has risen due to its effectiveness in limiting the need for seizure medication. Furth and colleagues performed both a retrospective case–control study of ketogenic diet participants and a prospective analysis of patients adhering to the diet [Furth *et al.* 2000]. The authors found a 15% incidence of renal stones in the case–control study. Data from 112 patients followed prospectively demonstrated a 5% incidence of stones in followup that ranged between 7 and 22 months. In the prospective cohort, spot urinalysis obtained from 16 patients revealed 2/3 had an elevated calcium creatinine ratio. Nine patients with a 24-hour urine study showed a significant decrease in citrate excretion following initiation of the diet [Furth *et al.* 2000]. Overall estimates of urolithiasis following the initiation of the ketogenic diet range between 3% and 10% [McNally *et al.* 2009; Kielb *et al.* 2000]. McNally and colleagues recently published a retrospective review of their group's use of oral potassium citrate prophylactically in children maintaining a ketogenic diet. In children prescribed potassium citrate only after the documentation of elevated calcium to creatinine ratio, the authors noted a 6.7% incidence of kidney stone formation. This incidence was significantly higher than the 0.9% incidence in children treated universally with potassium citrate irrespective of urinary calcium levels. Furthermore, 10.5% of children not receiving potassium citrate formed a stone compared with 2% of children receiving therapy [McNally *et al.* 2009]. In summary, ketogenic diet adherence appears to increase the risk of urinary stone disease. Treatment of children adhering to this diet with potassium citrate may be warranted.

Sex predilection

Classically, both adult and pediatric stone disease has been predominately a disease of male patients with an oft-quoted male:female ratio of 3 : 1 [Asper, 1984], yet theories of male predilection may be driven in part by the inclusion of historic series in which male bladder stones comprise a large portion of the population being studied [Rizvi *et al.* 2002]. Nonetheless, recent data have challenged the theory of a male predilection for urinary stone disease, and have further implicated increases in female urolithiasis as contributing to an overall increase in pediatric urolithiasis. Scales and colleagues scrutinized a population of adult stone patients from 1997 to 2002 finding the male:female ratio had decreased from 1.7 : 1 to 1.3 : 1. During the study period, overall inpatient stone discharges rose 5.7%, and female stone discharges rose an average of 22% compared with no change in males [Scales *et al.* 2009]. Additional work by Strope and colleagues revealed that between 1998 and 2004, utilization of hospital services for stone disease increased at a significantly faster pace among adult female patients [Strope *et al.* 2010].

In two reports, investigators from Johns Hopkins in Baltimore, MD, utilized the Kids Inpatient Database (KID) to evaluate stone prevalence according to patient sex. In the first report, Novak and colleagues provided a 1-year snapshot of over 2 million pediatric hospitalizations. During the time frame studied, 70% of pediatric admissions for stones were in female patients. The authors noted a higher prevalence of stone disease in male patients during the first decade of life while a higher female prevalence was observed in the second decade of life [Novak *et al.* 2009]. In the second report, the authors studied nephrolithiasis admission rates during the years 1997, 2000 and 2003. Notably, over time, a 365% increase was observed in female stone diagnosis and a 274% increase among males. Again, in the first decade of life, males were more commonly affected than females, and this finding reversed during the second decade of life [Matlaga *et al.* 2010]. Finally, a report utilizing a registry of all emergency department visits in the state of South Carolina from 1996–2007 demonstrated that among children, emergency department visits for stones rose at a significantly faster rate in females [Sas *et al.* 2010]. Suggested theories for increased female urolithiasis most often come from the adult literature and include differences in the hormonal milieu and increases in female obesity, but it remains unclear whether these theories apply to pediatric patients.

Incidental diagnosis

Another potential cause for increases in pediatric urolithiasis is the increased use of advanced imaging studies such as computed tomography (CT) for the evaluation and management of not only urinary stone disease but also nonurologic abdominal complaints. A recent review by Stratton and colleagues highlighted the dramatic increase in the utilization of CT imaging in children since the 1980s. According to the article, a 96% increase in the number of CT scans for children less than 15 occurred between 1996 and 1999 [Stratton *et al.* 2010]. Smaldone and colleagues purported that a stage migration of urinary stone disease is occurring due to the diagnosis of smaller ureteral stones as opposed to large renal or bladder stones [Smaldone *et al.* 2007]. Such a change may be due to the increased use of complex imaging techniques such as CT. In a Canadian series of pediatric urolithiasis, more than 50% of patients underwent CT imaging and 21% of patients were diagnosed with urolithiasis incidentally [Kit *et al.* 2008]. However, the relative paucity of clear data regarding the number of incidentally diagnosed pediatric urolithiasis makes conclusions regarding epidemiologic contribution of increased CT utilization difficult to confirm. Yet, what is known with relative certainty is that the number of CT scans performed in children has dramatically increased in recent years, particularly in the evaluation of urolithiasis. In several recent retrospective series, up to 54% of children presenting with urinary stone disease will undergo a CT during their workup for abdominal pain [Kalorin *et al.* 2009; Kit *et al.* 2008; VanDervoort *et al.* 2007]. Another review using the PHIS data set spanning 1999 to 2008 revealed a nearly 20% increase in the performance of CT scans during the evaluation of patients admitted for nephrolithiasis. In addition, 79% of children undergoing a CT had two or more studies performed [Routh *et al.* 2010b].

The combination of improved endourologic techniques and incidental diagnosis of urinary calculi may be impacting epidemiologic characteristics of pediatric urolithiasis by influencing the referral patterns of patients. No direct data are present in the literature to suggest that the miniaturization of endourologic instruments and the refinement of endourologic techniques have affected referrals to pediatric urologists or the subsequent treatment of pediatric stone disease. However, it does seem plausible that the incidental diagnosis of smaller asymptomatic stones by CT combined with the advancement of minimally invasive endourologic techniques may have lead to an increase in the treatment of small stones that may otherwise have been observed. For example, in a review of Pakistani children with nephrolithiasis by Rizvi and colleagues, the authors compared surgical management of stones in 486 children over an 8-year period from 1987–1995 and in 904 children over a 4-year period from 1996–2000 [Rizvi *et al.* 2003]. Only 50 minimally invasive stone procedures were performed in period 1 while 386 were performed in period 2. Most likely, the total number of stone procedures performed increased as a result of improved minimally invasive techniques rather than a marked and rapid increase in the number of stone forming patients. Unfortunately, stone size and location data were not provided by time period so these characteristics could not be compared. In the future, studies may need to examine the treatment patterns of pediatric urolithiasis and the relationship to stone presentation, stone size and treatment modality.

Comorbid illness

A small number of studies have begun to implicate medical comorbidity as a contributor to the formation of urolithiasis. Investigators from Johns Hopkins utilized the KID for the individual years 2003 and 2006. The pooled data encompassed over 6 million subjects and allowed for the evaluation of a relationship between medical comorbidity and stone presentation. Older age at presentation was found to be a strong predictor with children between the ages of 16 and 20 having the highest stone incidence. The authors suspected some interaction was occurring between age and comorbid conditions such as hypertension and diabetes. Multivariate modeling, controlling for age, demonstrated that hypertension in children less than 10 and diabetes in children less than 5 were strong, significant risk factors for urolithiasis development. Interestingly, in the models, obesity was not a significant risk factor for stone disease [Schaeffer *et al.* 2010]. A German study in adult stone patients found a similar association between urolithiasis and diabetes [Zimmerer *et al.* 2009], yet additional studies in children to corroborate these findings are absent from the literature. It has been suggested that insulin resistance leads to lower urinary pH and uric acid crystallization [Daudon *et al.* 2006; Pak *et al.* 2003]. Altered insulin sensitivity may also lead to calcium urolithiasis by promoting hypocitraturia [Cupisti *et al.* 2007]. Although pediatric patients with hypertension and diabetes likely represent a small subset of children with stones, it may be worthwhile for future studies of pediatric urolithiasis to address such comorbid diseases.

Conclusions

Accumulating evidence indicates that pediatric urolithiasis is increasing in prevalence, primarily in developed countries. However, well-designed epidemiologic studies are needed to confirm these assumptions. All of the proposed theories provided here are plausible explanations for increases in pediatric stone disease. It is unlikely that one factor will be solely responsible. The only way for the field of pediatric urology to advance its understanding of urolithiasis during childhood is to undertake improved research.

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