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American and Brazilian Children With Primary Urolithiasis: Similarities and Disparities

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Abstract

Objectives. Considering the differences in location, socioeconomic background, and cultural background, the aim of this study was to try to identify possible factors associated with the increased incidence of urolithiasis by comparing American and Brazilian children with stones. **Methods.** Data of 222 American and 190 Brazilian children with urolithiasis were reviewed including age, gender, body mass index, imaging technique used (ultrasound and computed tomography), and 24-hour urine volume and chemistries. **Results.** There were no differences between age and gender at diagnosis. Brazilian children were leaner but in no population did obesity rate exceed that of the general population. Ultrasound was most commonly used to diagnose stones, even more so in Brazilians. Decreased urine flow was more common among Americans ($P = .004$), hypercalciuria among Brazilians ($P = .001$), and elevated Ca/citrate ratio among Americans ($P = .009$). There were no differences between the groups in the frequency of hypocitraturia, hyperuricosuria, absorptive hyperoxaluria, and cystinuria. **Conclusions.** Despite some differences between the populations, the leading causes of urolithiasis among both were “oliguria,” hypercalciuria, and high Ca/citrate ratio. In neither country was obesity the reason for the increase in incidence of urolithiasis, nor was the use of computed tomography. The similarities between the 2 populations call for combining efforts in addressing the leading causes of pediatric urolithiasis.

Keywords

kidney stones, epidemiology, urine flow, hypercalciuria, hypocitraturia

Introduction

Pediatric urolithiasis has become more common over the past few decades.¹⁻³ Although the mechanisms underlying this observation remain to be determined, it has been attributed to global warming, lifestyle changes, nutritional habits, and possibly other environmental factors.^{2,4}

Additional factors that were considered are obesity, now shown to be a contributing factor in adults, and the increased use of computed tomography (CT).^{3,5} Obesity, via insulin resistance, is causing a decrease in tubular ammonium production, leaving more H⁺ ions to remain free and thus lower urine pH.⁶ The latter promotes precipitation of uric acid and stone formation.⁶ As for CT, its increased availability and use may have by itself resulted in more frequent diagnosis of kidney stone disease but this matter is still in debate.^{3,4}

Global warming resulting in decreased urine output and changes in dietary factors with increase in consumption of salt-rich processed food and decrease in potassium-rich natural ones, leading to hypercalciuria and hypocitraturia, have also been considered as contributors to the phenomenon.⁷ However, at this point more information is required to substantiate the aforementioned proposals. Moreover, the etiology of pediatric

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stone disease may vary from place to place depending of genetic and environmental factors.^{1,7-12}

In the present study, we thought to take the opportunity to study 2 populations diversified by geographic location and cultural and socioeconomic factors, as discussed below, to learn whether any differences in stone etiology between them might provide further insight into the factors associated with the universal increase in pediatric stone disease.

Methods

The study was a cohort of children and adolescents (0-19 years) with primary urolithiasis seen at Children's Mercy Hospital and Clinics at Kansas City, Missouri, USA (latitude 39°06"N), and at Clinics Hospital at Belo Horizonte, Minas Gerais, Brazil (latitude 19°55"S), between January 1999 and December 2010. Kansas City metropolitan area includes 1.8 million people, and Children's Mercy Hospital is the only pediatric referral center for the metropolitan area and surrounding counties. The metropolitan area of Belo Horizonte has 5 million inhabitants, and the Clinics Hospital at Belo Horizonte is the only pediatric referral center for the whole state.

Participants: Inclusion and Exclusion Criteria

Patients were identified by reviewing computerized registries of hospital discharge diagnoses at participating institutions. Patients were included in the study if the review of their medical records confirmed the diagnosis of a kidney stone based on clinical features and on documented primary kidney/ureter stone(s) by renal ultrasonography (US) or CT. Medical records were reviewed for clinical data including age at diagnosis, gender, weight, height, and body mass index (BMI), and the imaging technique used to diagnose urolithiasis. Overweight and obesity were defined according to the World Health Organization criteria (BMI z score > 2). All patients had serum and 24-hour urine analyses. Urine collection accuracy was validated by urine creatinine excretion rate, according to Hellerstein et al.¹³ The 24-hour urine sample analysis included volume, creatinine, calcium, uric acid, citrate, oxalate, and cystine. The blood sample analysis included creatinine, uric acid, calcium, phosphorus, magnesium, chloride, sodium, potassium, and bicarbonate.

Patients with a secondary cause of urolithiasis such as prematurity, Crohn's disease, cystic fibrosis, or use of topiramate, furosemide, or corticosteroids, and those with inaccurate collection were excluded. All evaluations were performed at least 1 month after diagnosis

Table 1. Abnormal Biochemical Values in 24-Hour Urine in Children.

	Abnormal Value
Urine output	<1.0 mL/kg/h
Calcium	>4.0 mg/kg/24 h
Citrate	<180 mg/g creatinine
Calcium/citrate ratio	>0.33 mg/mg
Uric acid	>815 mg/1.73 m ² /24 h
Oxalate	>52 mg/1.73 m ² /24 h
Cystine	>60 mg/1.73 m ² /24 h

and stone(s) passage, while participants were asymptomatic and on their usual diet and physical activity. Standard laboratory assays were employed for determination of the above-mentioned analytes, and the normative data used for urine chemistry were the same for the 2 populations. Criteria used to indicate abnormal urinary findings are shown in Table 1. Patients were classified with idiopathic absorptive hyperoxaluria when they were submitted to a low oxalate diet and they had normal oxalate urinary excretion.

Statistical Methods

The following statistical tests were used for comparison between groups: the Mann-Whitney U test and t test for unpaired samples when normality conditions were fulfilled and the Wilcoxon test when they were not. Statistical analysis was conducted with SPSS version 18.0 (SPSS, Chicago, IL), and P value $< .05$ was considered statistically significant.

Ethical Considerations

The study was approved by the institutional review board of the Children's Mercy Hospital and Clinics (approval number IRB#11 03-039E) and by Clinics Hospital of the Federal University of Minas Gerais at Belo Horizonte (approval number ETIC 036/00), and the study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The parents or legal guardian(s) of each patient signed a written informed consent form, and assent was obtained from the patient.

Results

Of the 278 American patients identified, 45 with secondary causes of urolithiasis and 11 with inaccurate urine collection were excluded. Of the 236 Brazilian patients identified, 33 with secondary causes of urolithiasis and 13 with inaccurate urine collection were

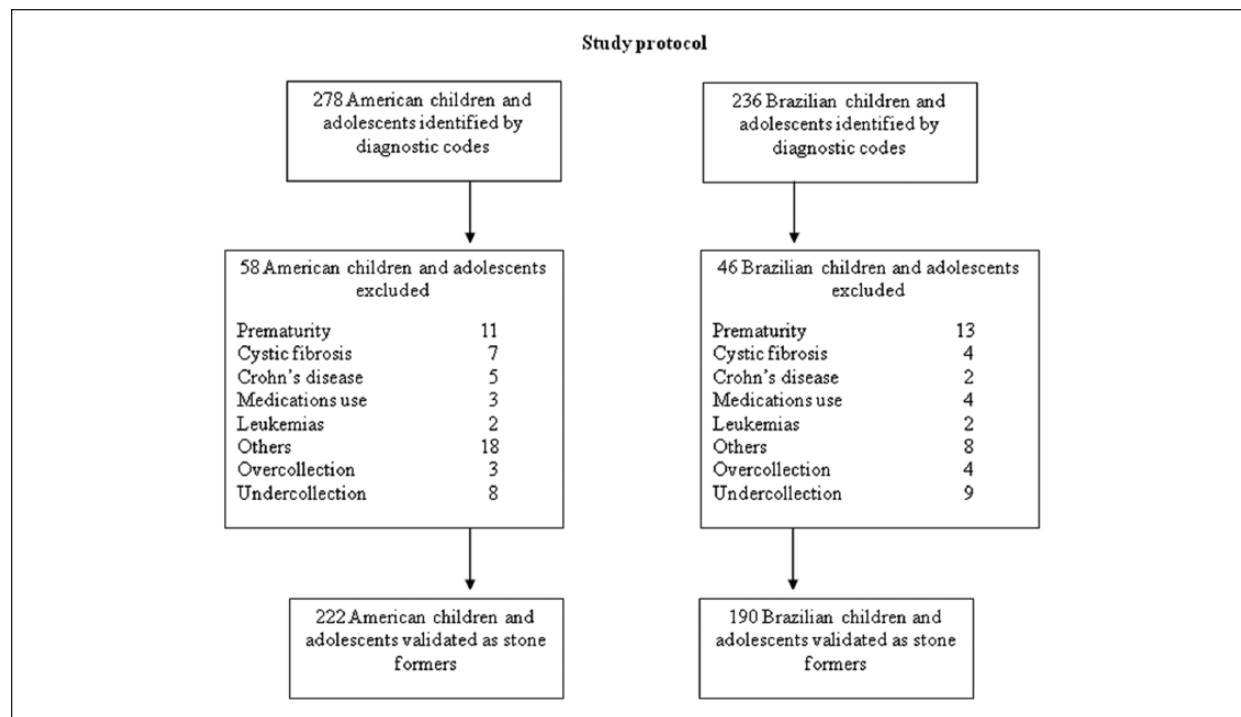


Figure 1. Study protocol of validation of pediatric stone formers in Children's Mercy Hospital and Clinics at Kansas City, Missouri, USA, and at Clinics Hospital at Belo Horizonte, Minas Gerais, Brazil, between January 1999 and December 2010.

excluded. Thus, the study samples consisted of 222 American and 190 Brazilian children and adolescents (Figure 1).

No abnormalities were noted in serum chemistries in either group. As shown in Table 2, the mean age at diagnosis was 11.8 ± 3.8 and 8.2 ± 3.2 years in American and Brazilian children, respectively, showing a trend for Brazilian children to be younger at diagnosis, which however did not reach statistical significance. There was no difference in gender distribution between the 2 groups. Brazilian children were on average leaner and significantly fewer were overweight. In all children stone diagnosis was mostly done by US rather than CT, even more so in Brazil.

The leading causes of urolithiasis in both populations were decreased urine output, hypercalciuria, and elevated urine Ca/citrate with some differences between the 2 populations, with low urine flow more frequent in American children, hypercalciuria in Brazilian children, and high urine Ca/citrate among the American ones. The frequency of hypocitraturia was the same in both groups as were those of hyperuricosuria, hyperoxaluria, and cystinuria, with the latter 2 conditions being quite uncommon in both populations. In similar percentages of children no abnormality was detected. On the other hand, in some children more than one abnormality was observed.

Discussion

It is by now very well documented that in recent years there has been a significant increase in the incidence of urolithiasis among adults and children.^{1-4,14,15} Among the reasons implicated in this rise are the introduction of CT to the emergency department and its frequent use in the evaluation of patients with abdominal and flank pain, obesity, global warming, and dietary changes.^{3,5,16-18} In the present study, we aimed to learn whether comparison of 2 pediatric populations from different latitudes and different socioeconomic and cultural backgrounds might shed additional light on the etiology of pediatric urolithiasis in primary stone formers. As mentioned earlier, the 2 participating institutions are the sole providers in their geographic areas for children with urolithiasis. They are located at significantly different latitudes and their populations experience different levels of income and development. As such whereas in Kansas City the climate is temperate or subtropical, it is humid subtropical (humid summers and generally mild winters) in Belo Horizonte. The US gross domestic product (GDP) in 2010 (study period) was US\$14.9 trillion, and the human development index (HDI) was 0.902. Brazil's GDP in 2010 was US\$2.18 trillion, and the HDI was 0.699.

Several authors have suggested that the increase in stone incidence in recent years might be attributed to the

Table 2. Demographic and 24-Hour Urine Biochemistries in American and Brazilian Children With Urolithiasis^a.

	American Children (n = 222)	Brazilian Children (n = 190)	P
Age at diagnosis (years)	11.8 ± 3.8	8.2 ± 3.2	NS
Male	48%	51%	NS
BMI z score	0.36	0.01	.001
Overweight (z score > 2)	15%	2%	.00001
Imaging technique US/CT	73%/27%	98%/2%	.001
Low urine output	63%	49%	.004
Hypercalciuria	47%	69%	.001
High calcium/citrate ratio	54%	41%	.009
Hypocitraturia	10%	9.5%	NS
Hyperuricosuria	6.4%	9.5%	NS
Idiopathic absorptive hyperoxaluria	1.4%	1.6%	NS
Cystinuria	0.5%	1.0%	NS
No abnormality	9.0%	13.0%	NS

Abbreviations: BMI, body mass index; US, ultrasound; CT, computed tomography.

^aQuantitative abnormal values are provided in Table 1. In some children more than one abnormality was detected.

more frequent use of CT.^{3,19} The study by Dwyer et al supported this hypothesis, based on their finding that the increased diagnosis of stone was associated with a parallel increase in the use of CT.³ However, Clayton and Pope reported that only 7% of their patients required nonenhanced CT for the diagnosis of urolithiasis after US or radiography failed to detect kidney stones.⁴ Spivacow et al¹⁰ detected stones by US in 77% of their pediatric stone population in Argentina, a figure almost identical to the finding in the American group in the current study (Table 2). Furthermore, in the Brazilian arm of our study US was utilized almost exclusively. Thus, it seems that our findings and others support the suggestion that there is an increase in stone incidence. It is very possible that the more frequent use of CT and changes in environmental factors (vide infra) both contribute to the increased incidence of urolithiasis.

Mounting evidence within the adult literature shows a causal relationship between obesity and kidney stone formation.^{5,6,20} Obesity has reached an epidemic stage, and the risk for stone formation increases with the increase in BMI, noticed when the BMI is >30 kg/m².²⁰ The pathophysiology is thought to be a decrease in tubular ammonia generation due to insulin resistance. Consequently, more hydrogen ions remain free, maintaining low tubular pH that promotes the formation of uric acid stones.^{6,20} While adult urolithiasis is clearly linked to obesity, studies of pediatric patients have not shown such an association. In the largest pediatric case series to date exploring the role of BMI in pediatric stone formers, Kieran and colleagues found no data to support a direct role of high BMI in the presentation or treatment of kidney stones.¹⁷ Additional studies on

pediatric urolithiasis reached the same conclusion.^{3,21} In the current study, although American children were heavier (Table 2), the percentage of those being overweight did not exceed the percentage in the general pediatric school-age population of 17.0% per recent data from the Centers for Disease Control and Prevention.²² Although national data regarding obesity in the Brazilian pediatric population were not fully available, a recent school-based cross-sectional study by Silva et al²³ involving 41 654 students showed that the growth in body weight, height, and BMI in urban areas is increasingly similar to those reported in developed countries. It is thus possible that body weight in stone forming children is a reflection of that in the general population in that location, and it is not by itself a cause for the increase in incidence of urolithiasis in the pediatric population in either country.²³

The incidence of mild idiopathic absorptive hyperoxaluria and cystinuria were very low in both populations. Other studies have shown a greater incidence of hyperoxaluria, ranging from 5.1% to 26.5%.^{2,7-9} It is possible that differences in incidence between our study and others in regard to hyperoxaluria may depend on the genetic makeup and dietary habits of different populations. As for hyperuricosuria, in all our patients it was of low magnitude and associated with other biochemical abnormalities such as hypercalciuria and hypocitraturia. Furthermore, in a previous study in which stone analysis was conducted in the American center of the current study, all stones were found to be composed of calcium oxalate and/or phosphate without a component of uric acid.⁹ Therefore, it might be that at least in some patients mild hyperuricosuria is a coincidental finding rather

than the etiology of urolithiasis. Further research into this issue might be required.

Although there were some differences between the 2 groups in their frequencies, the most common abnormalities were “oliguria,” hypercalciuria, and hypocitraturia, with the combination of the latter 2 conditions resulting in high urine Ca/citrate ratio. The importance of adequate fluid intake has been demonstrated already in the past, as well as the effect of hot climate on increase in stone incidence likely due to decreased urine output.^{16,24,25} Urine flow of less than 1.0 mL/kg/h has been shown to be associated with increased supersaturation of calcium oxalate and calcium phosphate.^{24,25} Considering that 63% of American children and 49% of Brazilian children presented with such “oliguria,” we strongly believe that urine output must be closely monitored. Higher fluid intake can be an inexpensive worldwide public health goal, and fluid intake should further increase in areas of hot climate and in all areas in hot days.^{16,26} Indeed, following orders, an increase in fluid intake in US Army soldiers stationed in a high environmental temperature zone resulted in a decrease in the incidence of urolithiasis.²⁷

Stone composition and abnormal urinary biochemical profiles vary worldwide, depending on genetic factors at times including consanguinity, local nutritional and drinking habits, environmental factors, and prevalence of urinary tract infections.^{7,8,11,12,28} However, in most studies hypercalciuria is the predominant biochemical abnormality.^{1,9-12} Similarly, hypercalciuria was found in 69% of our Brazilian patients and in 47% of the Americans (Table 2). As recently shown by Srivastava et al,²⁹ although the finding of hypercalciuria is of utmost importance, by itself it may not always explain the tendency for stone formation unless urine citrate is factored in, due to the fact that the latter provides protection against formation of calcium stones. Hypocitraturia was encountered in 10% of our Americans and 9.5% of Brazilian children; however, many more children in both populations were found to have high Ca/citrate ratio. Several studies have now shown urinary Ca/citrate ratio to be a sensitive indicator for the risk of stone formation, and Defoor et al³⁰ demonstrated it to be superior to all other urinary biochemical parameters in assessing the risk for recurrent stone formation. As indicated in Table 1, this parameter has the advantage of being independent of urine volume, creatinine, or other common denominators. Based on our and others' finding, it is evident that further research is required to identify the reasons for the large number of children having high urinary calcium and/or low citrate, resulting in high Ca/citrate ratio and consequently high risk for stone formation.

Our study has several limitations including being retrospective and for not analyzing stone composition. The reason for the latter was that in recent years stones are captured and analyzed only in a minority of patients. In the majority of patients the diagnosis is made in the emergency department and the patients are being sent home on medical therapy. In most cases the stone is expelled at home without being captured and analyzed. As such, we felt that inclusion of a small number of analyzed stones may result in a statistical bias. Another limitation was the lack of data regarding urinary sodium/potassium ratio that was demonstrated to be associated with hypercalciuria. Unfortunately, this urine analysis was not always done in earlier years and hence, if added, would have skewed the data. The strengths of our study include the large number of pediatric patients studied by the same protocols, methodologies, and norms used for blood and urine chemistry and the novelty of the comparison between 2 geographically and culturally diverse populations.

In summary, despite some differences between the studied populations, the leading causes of urolithiasis among both American and Brazilian children were “oliguria,” hypercalciuria, and high Ca/citrate ratio. In neither country was obesity per se more frequent in stone patients compared with the general population. The preferred imaging technique was US, excluding more frequent use of CT as the only reason for the increase in incidence of pediatric urolithiasis. The aforementioned findings indicate the need for continuous research to identify the causes of hypercalciuria and hypocitraturia and means to correct them, as well as the need to educate the population worldwide about the importance of high fluid intake in order to achieve adequate urine flow. Furthermore, the finding of near similarity between the 2 populations studied calls for combined efforts in addressing these challenging matters.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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