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Kidney Stones and the Ketogenic Diet: Risk Factors and Prevention

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A cohort study was performed of children started on the ketogenic diet for intractable epilepsy from 2000 to 2005 (n = 195). Children who developed kidney stones were compared with those without in terms of demographics, urine laboratory markers, and intervention with urine alkalinization (potassium citrate). Thirteen children (6.7%) developed kidney stones. The use of oral potassium citrate significantly decreased the prevalence of stones (3.2% vs 10.0%, $P = .049$) and increased the mean time on the ketogenic diet before a stone was first noted (260 vs 149 patient-months, $P = .29$). The prevalence of kidney stones did not correlate with younger age or use of carbonic anhydrate inhibitors (eg, topiramate or zonisamide) but trended toward higher correlation with the presence of hypercalciuria (92% vs 71%, $P = .08$). No child stopped the diet due to stones; in fact, the total diet duration was longer (median 26 vs 12 months, $P < .001$). Kidney stones continue to occur in approximately 1 in 20 children on the ketogenic diet, and no statistically significant risk factors were identified in this cohort. As oral potassium citrate was preventative, prospective studies using this medication empirically are warranted.

Keywords: kidney stones; ketogenic diet

The ketogenic diet is a high-fat, moderate-protein, and low-carbohydrate diet that, by increasing the oxidation of fatty acids and subsequent production of ketone bodies, places the patient in a state of ketosis and acidosis.[1-3] In multiple studies, it has been shown to be efficacious for intractable childhood epilepsy.[1,3] Nephrolithiasis has been observed in children receiving the ketogenic diet since it was first reported more than 30 years ago.[4] The prevalence of kidney stones ranges from 3% to 10%, in comparison to 1 in several thousand in the general population.[5,6]

There are several reasons for this increased risk. Hypercalciuria occurs with the ketogenic diet due to increased bone demineralization with acidosis (bone phosphate acts as an acid buffer) as well as increased calcium excretion by the kidney.[6] Children on the ketogenic diet are also more likely to have hypocitraturia; as citrate normally solubilizes free calcium in the urine, less citrate in the urine means that more free calcium is available for stone formation.[7] In addition, as uric acid is less soluble in the low urine pH seen in children on the diet, it may more readily form crystals and act as a nidus for calcium stone formation.[7] Lastly, children on the ketogenic diet are traditionally fluid restricted to 80% of estimated daily needs.

A previous study examining risk factors for nephrolithiasis in children on the ketogenic diet from 1996 to 1999 suggested the potential benefits of alkalinization of the urine using oral potassium citrate in children with a urine calcium to creatinine ratio >0.20 mg/mg.[6] Potassium citrate solubilizes calcium, thereby decreasing concentration of free calcium available to crystallize, and also increases urine pH, allowing uric acid crystals to dissolve.[8,9] A study in 2002 indicated that children on carbonic anhydrase inhibitors and the ketogenic diet with positive family histories of kidney stones are at increased risk and also should be treated.[10] Based on these 2 studies, we began to measure urinary calcium to creatinine ratios at baseline ketogenic diet initiation and every 3 to 6 months and treated children with oral potassium citrate (Polycitra K) at a dose of 2 mEq/kg/day, divided twice daily if the urine calcium to creatinine ratio was >0.20 mg/mg, they had symptoms of a kidney stone, or there was a family history of nephrolithiasis and were receiving a carbonic anhydrase inhibitor. In this cohort, we reexamined risk factors and if initiation of potassium citrate would reduce the incidence of kidney stones.

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Methods

A retrospective cohort study was performed of all children started on the ketogenic diet at our institution over a 5-year period, from January 1, 2000, to December 31, 2005, with at least 1-month follow-up. Children were fasted for 24 to 48 hours, then gradually started on increasing calories of either a 3:1 or 4:1 (fat to protein and carbohydrates) ratio with caloric restriction generally to 75% of the estimated daily needs to maintain an ideal body weight and fluid restriction to 80%.[3] Children were typically seen in the clinic every 3 to 4 months for the first year, every 6 months thereafter, and followed by phone and e-mail correspondences during the interim periods to monitor seizure control, medications, laboratory values, and adverse effects. Serum electrolytes and urine calcium to creatinine ratios were ordered at baseline and subsequently every 3 to 6 months just prior to all clinic visits. Parents were also instructed to test the urine at home for hematuria and ketones at least weekly using Bayer Multistix SG (Bayer Corporation, Elkhart, Ind). Urine citrate and pH were not routinely measured.

The presence of kidney stones was defined as (1) stones or stone fragments found to have been passed in urine or noted in the diaper, (2) gross or microscopic hematuria concurrent with lower flank pain, or (3) evidence on ultrasound or computed tomography scan of a stone or nephrolithiasis. Hypercalciuria was defined as a urine calcium to creatinine ratio >0.20 mg/mg. Children were considered immobile if they spent the majority of their time in a wheelchair or stroller past 2 years old.

Categorical data were analyzed using the Fisher exact test for independence of rows and columns. Numerical data were analyzed by using the Wilcoxon rank-sum test. The significance level for all tests was $P = .05$.

Results

Over the 6-year period, 197 children with intractable epilepsy, median age 3 years (range, 0.5-15 years), were started on the ketogenic diet. Two children discontinued the diet prior to 1 month and were excluded from analysis. Children had attempted a median of 5 medications prior to diet initiation (range, 0-13 medications) and remained on the diet for a median of 12 months (range, 1-72 months). Fifty-six percent were on a 3:1 ratio at diet onset. In total, 107 (55%) children began potassium citrate during their time on the diet, with a median start time of 3 months on the diet. Ten of 106 were started as a direct result of a kidney stone being identified after starting the diet. Nine children stopped potassium citrate therapy for various reasons, including resolution of hematuria, a reduced urine calcium to creatinine ratio, and irritability.

Thirteen (6.7%) children developed kidney stones, presenting after a median of 7 months on the diet (range, 1-28 months). Information is provided in Table 1. This was not significantly different from the previously reported prevalence, in which 6 of 112 (5.4%) had stones ($P = .42$).[6] Twelve (92%) children had hypercalciuria and hematuria at the time of stone presentation. No child stopped the diet due to stones; in fact, the diet duration was longer in those with stones (median 26 vs 12 months, $P < .001$).

Table 2 summarizes the differences between children with and without kidney stones. The children without kidney stones were twice as likely to have been started on potassium citrate preventatively beforehand (50% vs 23%; $P = .049$). This translates into a prevalence of kidney stones of 3.2% (3 of 95) for those started on potassium citrate preventatively, compared with 10.0% (10 of 100) for those who were not. An analysis of patient-months on potassium citrate compared with those not on therapy showed that 1 stone occurred after 148 patient-months on the diet without therapy; potassium citrate extended the time to develop 1 stone to 260 patient-months, but this was not significant ($P = .29$). Those with kidney stones were somewhat more likely to have an elevated urine calcium to creatinine ratio detected while on the diet, but this did not reach statistical significance ($P = .08$). Only 1 child did not have an elevated urine calcium to creatinine ratio prior to developing a stone. Recurrent kidney stones occurred in 3 children; 2 had recurrences despite adding potassium citrate, and 1 was prescribed potassium citrate, but the parents discontinued it.

Urine calcium to creatinine ratios were available for review in 138 (71%) children during their time on the ketogenic diet. Although urine calcium to creatinine ratios were always ordered, they were not always performed due to patient incontinence, noncompliance, lost specimens or results, or incomplete analysis of the calcium to creatinine ratio by the laboratory. The median urine calcium to creatinine ratio at baseline was 0.20 mg/mg; this increased to 0.40 to 0.50 mg/mg after 3 to 12 months in all patients. An elevation in the urine calcium to creatinine ratio >0.2 mg/mg occurred in 101 (52%); 83 (82%) were started on urine alkalinization. Of the 18 patients with an elevated urine calcium to creatinine ratio who were not treated, 6 (33%) developed stones. The urine calcium to creatinine ratio did not decrease significantly for individual patients after potassium citrate was started; of the 36 children who had a follow-up urine calcium to creatinine ratio after oral alkalinization, 24 (67%) had a decrease of 0.05 mg/mg or more, and 12 (33%) had an increase. The mean urine calcium to creatinine ratio at the time of kidney stones was 0.94 mg/mg.

Discussion

This study clarifies the risk factors for kidney stones for patients on the ketogenic diet. Hypercalciuria was more common in those with kidney stones, although in this

Table 1. Patients With Kidney Stones on the Ketogenic Diet, Started 2000-2005 (n = 13)

Patient	Age at Diet Onset, y	Ketogenic Diet Ratio	Diet Duration at Time of Stone, Months	Symptoms at Presentation*	Urine Ca/Cr at Stone	Oral Potassium Citrate Prior to Stone?	Carbonic Anhydrase Inhibitor† Use
1	1.0	3:1	1	Stone (calcium oxalate), hematuria	2.9	No	Yes
2	1.0	3:1	7	Nephrocalcinosis, hematuria	4.0	Yes	Yes
3	1.0	4:1	28	Stone fragments	1.7	Yes	Yes
4	2.5	3:1	6	Stone	0.7	No	No
5	2.5	3:1	16	Hematuria, pain	1.0	No	No
6	3.5	4:1	9	Stone, hematuria	0.3	No	No
7	4.0	3:1	4	Hematuria, pain	0.5	No	No
8	5.0	4:1	12	Stone	0.5	No	No
9	5.0	3:1	3	Stone	1.2	No	Yes
10	8.0	3:1	3	Stone (uric acid), hematuria	0.3	No	Yes
11	8.5	3:1	4	Stone fragments, hematuria	0.6	No	No
12	9.0	3:1	8	Stone (calcium carbonate)	0.4	Yes	No
13	9.0	4:1	10	Hematuria, pain	0.1	No	No

*Stone composition listed in parentheses if analyzed.
†Topiramate or zonisamide.

Table 2. Characteristics of Children With and Without Kidney Stones (n = 195)

	Kidney Stones (n = 13)	No Stones Identified (n = 182)	*P* Value
Median age, y	4.0	3.0	.54
Male gender, n (%)	6 (46)	99 (54)	.39
Immobile, n (%)	5 (38)	42 (23)	.18
3:1 ratio, n (%)	9 (69)	101 (55)	.25
Caucasian race, n (%)	12 (92)	145 (80)	.24
Prior preventative potassium citrate therapy, n (%)	3 (23)	92 (50)	<.05
Concurrent carbonic anhydrase inhibitor use, n (%)*	5 (38)	77 (42)	.51
Urine Ca/Cr >0.20 mg/mg, n (%)	12 (92)	89† (71)	.08
Median eventual duration of diet, months	26	12	<.001

*Topiramate or zonisamide.
†n = 126 children with documented Ca/Cr and no stones.

study, this only trended toward significance, largely as a result of 1 patient.[6,9] The possible consequence of not treating hypercalciuria with potassium citrate in this study was high, with one-third later developing stones. Also, in contrast to the previous study, younger age at diet initiation was no longer a risk factor.[6] Despite independent risk, concurrent use of carbonic anhydrase inhibitors did not increase risk of stones, similar to a previous report.[10] The longer overall ketogenic diet duration in those with kidney stones likely reflects the lack of any negative impact of stone incidence on seizure control rather than a true association, as half of the cases occurred before 6 months on the diet.

This study demonstrates that urine alkalinization had a protective effect against the occurrence of kidney stones on the diet. Children receiving this treatment preventatively had one-third the incidence of those who did not and twice the diet duration until a stone would typically manifest. Any delay in the occurrence of stones by using potassium citrate could be helpful, as children may have discontinued the diet before they reached a point when stones were more likely to occur. Recent information suggests that the risk of kidney stones is as high as 25% in children on the diet over 6 years.[11]

There were several limitations to this study. For one, kidney stones were only defined clinically; possible asymptomatic or radiographic stones may have been missed. Second, there was no way to confirm family compliance with potassium citrate administration. Last, as this was a retrospective study, physician treatment practices, availability of laboratory results, and patient follow-up frequency varied.

As the prevalence of kidney stones has not decreased since 2000, we believe the results of this study suggest that modifications to diet management need to be instituted. We advise regular monitoring of the urine calcium to creatinine ratio in children on the diet, although as the percentage with abnormal results was high for all children, this may not be a sensitive risk factor. In addition, liberalization of fluid restrictions may be beneficial, although this was not specifically analyzed as a risk factor for this study.[12,13] Patients started on a modified Atkins diet for seizure control are encouraged to drink plenty of fluids, and to date, efficacy appears equivalent with no incidence of stones.[13] Last, as oral potassium citrate was preventative and has no clear disadvantages, we are currently investigating the empiric use of this medication in all children starting the ketogenic diet.

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