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ORIGINAL PAPER

The pathogenesis of calyceal diverticular calculi

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Abstract Controversy exists over whether metabolic factors or urinary stasis predominate in the pathogenesis of calyceal diverticular calculi. We performed a study to better define the effects urinary stasis and metabolic abnormalities have in the pathogenesis of calyceal diverticular stones. Twenty-nine patients who underwent percutaneous treatment of calyceal diverticular calculi were studied. All patients underwent 24 h urine collection to evaluate metabolic risk factors. In three patients, urine was sampled directly from the diverticulum for metabolic studies. The urinary stone risk parameters of the patients with calyceal diverticular stones (Tic SF) were similar to those of a well-characterized cohort of calcium oxalate stone formers (CaOx SF). When compared to a group of normal people, the Tic SF and CaOx SF were significantly more hypercalciuric and their urine was significantly more supersaturated with calcium oxalate. Urine aspirated directly from the diverticulum had the lowest SSCaOx when compared to ipsilateral and contralateral renal pelves. The urinary risk profiles of patients with diverticular calculi are similar to those of CaOx SF, suggesting a metabolic etiology of diverticular stones. However, the SS CaOx of urine aspirated directly from the diverticula is significantly lower than that of the renal pelves; these data support the hypothesis that urinary stasis significantly contributes to the pathogenesis of calyceal diverticular calculi. Taken together, it seems likely that calyceal diverticular calculi arise from a combination of metabolic abnormalities and urinary stasis.

Keywords Kidney · Calculi · Calyceal diverticula · Percutaneous surgery

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Introduction

Calyceal diverticula are nonsecretory, transitional-cell epithelium-lined cystic cavities within the renal parenchyma, diagnosed on 0.21–0.45% of routine intravenous pyelogram studies [1]. From 9.5 to 50% of calyceal diverticula have been reported to harbor calculi [2]. Patients with this condition can be challenging to treat, often requiring a percutaneous approach to achieve optimal outcomes [3, 4].

The etiology of calyceal diverticular calculi is controversial, with both urinary stasis and underlying metabolic abnormalities implicated as singularly causative factors [5, 6]. In fact, there is little scientific evidence to support either one of these tenets, although clinical studies do suggest a contributory role of metabolic factors in stone formation [5, 6]. The role of stasis, if any, in calyceal diverticular stone formation has yet to be established. We performed a study to define the potential role of urinary stasis in the pathogenesis of calyceal diverticular calculi.

Methods

All patients presenting to our institution with calyceal diverticular calculi were offered the opportunity to participate in an ongoing, Institutional Review Board (IRB)-approved, prospective study of the pathogenesis of calyceal diverticular calculi. All patients enrolled underwent a complete medical history and physical examination, and patients with systemic disorders such as primary hyperparathyroidism, sarcoidosis, vitamin D excess, hyperthyroidism, or renal tubular acidosis were excluded from further analysis. Patient demographic information, including detailed clinical stone history records and serum chemistry testing results, was obtained. The size of the calyceal diverticular cavity was calculated by measuring the area of the diverticulum on the largest representative slice on preoperative computerized tomography (CT) imaging.

Patients harboring calyceal diverticular calculi (Tic SF) were treated by a percutaneous approach that we have previously described [4]. In addition, those patients whose diverticula were considered to be of a sufficient size underwent direct sampling of fluid from the diverticular cavity. This technique required the placement of an 18 gauge needle directly into the diverticular cavity, and aspiration of fluid from the cavity (Fig. 1). In addition, for these patients, ureteral catheters were placed in a retrograde fashion into the ipsilateral and contralateral renal pelves, for the purpose of lateralized urine collection. The administration of intravenous fluids was limited until collection was complete, to avoid distorting urinary metabolic parameters. Urine was collected by gravity drip, and negative pressure was not used to facilitate aspiration. The urine specimens were collected simultaneously. These specimens were assessed for pH, calcium, oxalate, citrate, phosphate, uric acid, sodium, potassium, magnesium, sulfate, and ammonia. Supersaturations were calculated for calcium oxalate (SS CaOx), calcium phosphate (SS CaP), and uric acid (SS UA) using EQUIL 2 [7].

Following the percutaneous removal of all stone material it was confirmed that no renal papilla was present within the calyceal diverticula, and the diverticula were then ablated. Two 24 h urine samples were collected while patients were on a random diet for the measurement of volume, pH, calcium, oxalate, citrate, phosphate, uric acid, sodium, potassium, magnesium, sulfate, and ammonia. We again calculated SS CaOx, SS CaP, and SS UA using EQUIL 2 [7]. All urine collections were performed over 1 month following the percutaneous procedure.

For urine calcium, oxalate, citrate, volume, phosphate, uric acid magnesium, sodium, potassium, ammonia, sulfate, pH and SS CaOx, SS CaP, and SS UA, we compared the Tic SF to a group of 245 calcium oxalate stone formers (CaOx SF) and 162 normal people (*N*); these two contrast groups were drawn from the University of Chicago stone program [8]. Comparisons were made via general linear models with sex and urine creatinine as covariates for excretion rates and sex and weight for urine pH; for SS values we used only sex as a covariate. Post hoc comparisons between the three groups were made within each model.

In a sub-group analysis, we divided patients with calyceal diverticular calculi into those who did and did

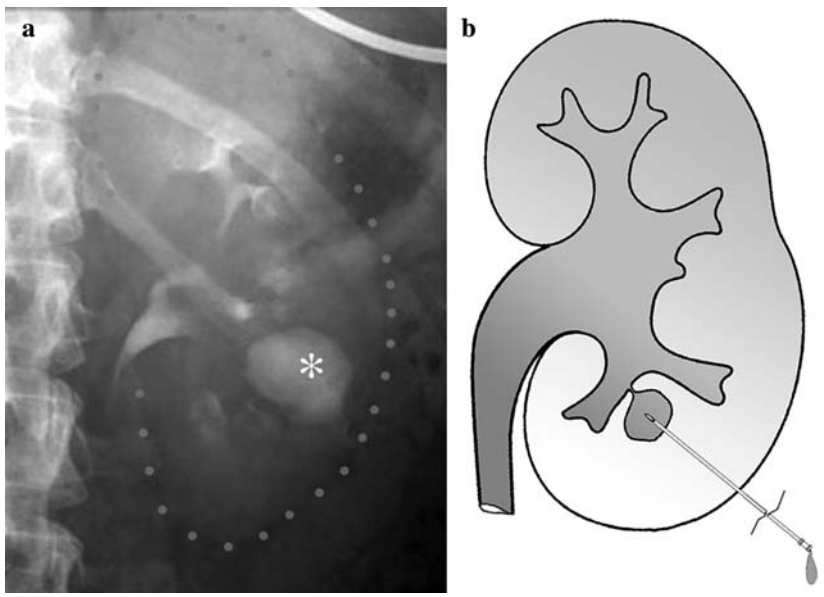

Fig. 1 **a** Intravenous pyelogram image of calyceal diverticulum (*asterisk*). **b** Cartoon schematic demonstrating aspiration of urine directly from diverticulum

not harbor additional renal calculi at the time of surgery, using the same linear modeling approach. Because no significant differences were found between these two subgroups, we do not present this analysis. Similarly, the Tic SF were divided into those with calcium oxalate stones and those with calcium phosphate stones, and again no significant differences were found between these two subgroups.

Results

Patient characteristics

From June 1999 to 2005, a total of 29 patients (9 males and 20 females, mean age 40 years) were enrolled in this study. Thirteen patients confirmed a history of prior stone events, and these 13 patients also harbored renal calculi in addition to calyceal diverticular calculi at the time of surgery. The remaining 16 patients had neither a stone history nor present kidney stones. Nine patients (31%) underwent prior attempted treatment of the calyceal diverticular stones, as follows: extracorporeal shock wave lithotripsy in five patients, ureteroscopy in two patients, and percutaneous nephrolithotomy in two patients. All of these procedures were performed at referring institutions. Stone analysis was performed in 20 cases; in certain cases, such as those patients with "milk of calcium" diverticular debris or those patients who had previously undergone SWL treatment which had pulverized the diverticular stone, it simply was not possible to extract stone material with a grasping device, or to filter and then retrieve the granules following evacuation with an ultrasonic lithotripter. In 15 cases stone analysis was predominantly calcium oxalate, in 4 cases stone analysis was predominantly calcium phosphate, and in 1 case stone analysis was uric acid. In all cases where patients harbored both diverticular and renal calculi, the stone material recovered from the diverticulum correlated with that in the renal collecting system. The mean diverticular size was 13.5 mm (range 3–44).

Primary urine stone risks

These data are presented as Fig. 2. Urine calcium of CaOx SF (241 mg/day) and Tic SF (237 mg/day) exceeded that of *N* (178 mg/day) (Fig. 2, upper left panel, $P < 0.001$ for both comparisons). Urine citrate values (Fig. 2, upper middle panel) did not differ among the groups. Urine pH was higher in Tic SF (6.1) than *N* (5.9) or CaOx SF (6.0) ($P < 0.05$ for both) (Fig. 2, upper right panel). Urine volumes (Fig. 2, lower left panel) did not differ between the groups. Urine SS CaOx (Fig. 2, lower middle panel) was higher in CaOx SF (9.6) and Tic SF (8.9) versus *N* (7.4) ($P < 0.01$ and <0.05, CaOx and Tic SF, respectively). Finally, SS CaP (Fig. 2, lower right panel) did not differ between groups.

Secondary urine measurements

Urine oxalate of CaOx SF exceeded *N* (Table 1) as did urine sodium, potassium, and sulfate of CaOx SF and urine potassium and sulfate of Tic SF (Table 1). These differences reflect diet effects.

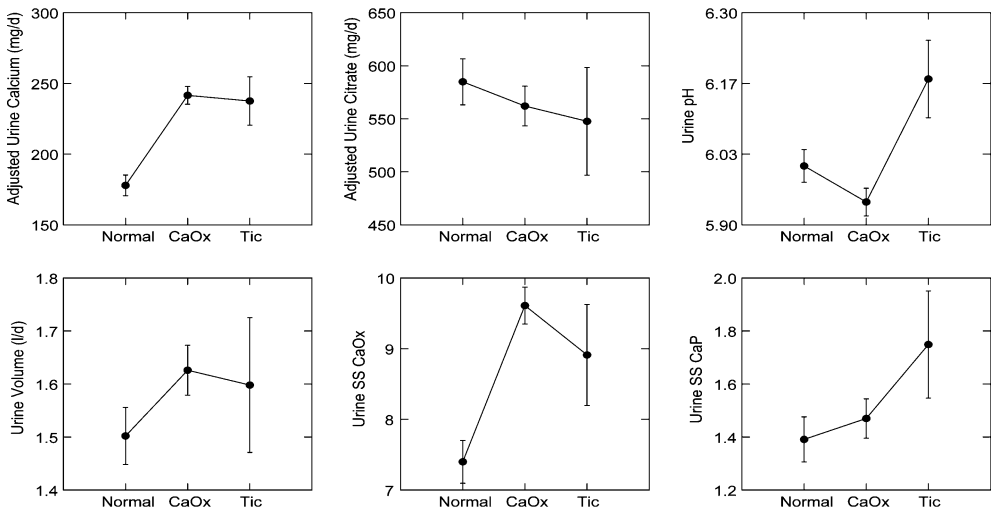

Fig. 2 Plots of adjusted primary urine stone risk parameters

Table 1 Supplemental urinary parameters

Urine measurement	Normals	CaOx stone formers	Diverticula patients
Oxalate (mg/day)	34 ± 1	38 ± 1[a]	38 ± 2
Uric Acid (mg/day)	640 ± 10	657 ± 9	640 ± 24
Sodium (mEq/day)	157 ± 4	173 ± 3[a]	174 ± 9
Potassium (mEq/day)	62 ± 1	54 ± 1[a]	53 ± 3[a]
Phosphate (mg/day)	886 ± 17	924 ± 15	917 ± 40
Magnesium (mg/day)	102 ± 3	100 ± 2	104 ± 6
Ammonia (mEq/day)	30 ± 2	30 ± 2	34 ± 3
Sulfate (mEq/day)	49 ± 2	42 ± 1[a]	40 ± 3[a]
SS uric acid	1.1 ± .0.1	1.3 ± 0.1	1.0 ± 0.2

Values are adjusted mean ± SEM

SS supersaturation

[a] Differs from normals, $P < 0.05$

Fluid samples from diverticula

Table 2 displays the results of the urine specimens collected by the novel technique of direct aspiration from the calyceal diverticula. These results are presented in conjunction with the urinary parameters measured from the ipsilateral and contralateral renal pelves. The data from these patients are remarkably similar; the urine aspirated directly from diverticulum contains the lowest SSCaOx when compared to the ipsilateral and contralateral renal pelves.

Discussion

Stasis of urine has traditionally been cited as a contributory factor in several conditions associated with an increased risk of stone formation, including calyceal diverticula and UPJ obstruction [6, 9]. Overall, though, there is little, if any, direct scientific evidence to support stasis as a contributing factor in the pathogenesis of urinary calculi. Frequently cited as supporting evidence for this tenet are the calculations of Finlayson and Reid [10] as well as those of Kok and Kahn [11]. However, these calculations were not based on direct experimental observations, but rather on theoretical computations. Building to a great extent on this work, Finlayson and colleagues asserted that diverticula, foreign bodies, and residual urine, all conditions that increase particle retention, will predispose a patient to urolithiasis. Similarly, Hinman [12] stated that the restriction to passage of a juvenile stone is a prerequisite to growth and depends on the configuration of the infundibulum or UPJ.

Calyceal diverticula, as Finlayson noted, are an example of impeded urinary drainage, and despite his and others' work on this subject, controversy still persists regarding the pathogenesis of stone formation in patients with these anomalies. Although Burns and Finlayson [13] have suggested that particle retention time in the setting of a diverticulum could be the cause of stone formation, others who have analyzed metabolic data have drawn conflicting conclusions. Over three decades ago, Timmons and associates [14] studied 28 patients with calyceal diverticula, of whom 4 had stones. Of the four patients with stones, one had hypercalciuria and another had a systemic disorder associated with urolithiasis (primary hyperparathyroidism). Liatsikos examined 49 patients with calyceal diverticular stones and compared their metabolic data to that of 44 renal stone formers [6]. They found that 25% of patients with calyceal diverticular stones had metabolic abnormalities compared to 77.3% of those undergoing PNL for other indications. In contrast, Hsu and Streem [5] studied 14 patients with calyceal diverticular stones treated with SWL and noted significant metabolic risk factors for stone formation in half of the group. However, approximately half of the patients in this study had previously formed calcium calculi.

Our findings suggest a metabolic component to the pathogenesis of calyceal diverticular calculi, insofar as the urinary risk parameters of the CaOx SF cohort were remarkably similar to those of the Tic SF. Specifically, the Tic SF patients were just as hypercalciuric as the CaOx SF. The hypercalciuria of the Tic SF cohort

Table 2 Urine aspirated directly from diverticula

Urine measurement	Patient 1			Patient 2			Patient 3		
	Tic	Ipsi	Contra	Tic	Ipsi	Contra	Tic	Ipsi	Contra
SS CaOx	4.71	6.07	11.16	2.49	3.64	3.38	0.13	0.14	N/R
SS CaP	0.35	0.39	0.75	0.91	0.84	1.26	0.18	0.39	N/R
Calcium	6.30	6.80	11.10	8.28	11.00	10.23	3.80	4.98	5.59
Oxalate	2.30	2.87	4.35	1.08	1.36	1.41	0.10	0.19	N/R
Citrate	8.72	9.80	13.50	27.43	45.89	45.26	75.4	79.9	N/R
pH	6.58	6.24	6.46	6.58	6.25	6.59	5.97	6.79	N/R
Stone analysis	Calcium oxalate			Calcium oxalate			Calcium oxalate		

Tic calyceal diverticulum, *Ipsi* psilateral renal pelvis, *contra* contralateral renal pelvis, *N/R* insufficient urine recovered for measurement

was also reflected in the increased SS CaOx values, and these changes persisted even when the Tic SF patients were sub-categorized into those harboring additional renal calculi at the time of surgery and those with stones in the diverticula alone. Auge and associates [15] have reported in a smaller series of patients that patients harboring calyceal diverticular stones may be found to suffer from hypercalciuria, hypocitraturia, and low urine volume, findings which also suggest a metabolic contribution to stone formation.

We cannot definitively explain the female preponderance in our present cohort of Tic SF, although similar findings were noted by Liatsikos' group [6] and Hsu and Streem [5]. It is possible that there is a referral bias in our patient population that may account, in part, for this discrepancy. We are similarly puzzled by the elevated urinary pH of the Tic SF. We cannot fully explain this phenomenon, as excluding the calcium phosphate stone formers did not significantly change this parameter. Unfortunately, others who have studied Tic SF have not reported the urinary pH of their study groups [5, 6], although Auge and associates [15] have reported similarly elevated urine pH in Tic SF.

The urine specimens aspirated directly from the calyceal diverticula are important to our understanding of the pathogenesis of calyceal diverticular stones, as they provide data that are not otherwise easily obtainable (Table 2). Direct sampling of the fluid from the diverticular cavity provides a unique assessment of the environment associated with stone formation in these examples of impeded urinary drainage. Our evaluations of the patients' 24 h urine collections, just as the evaluations presented in the previously reported studies, were all of voided urine. As voided urine collections include urine from both the ipsilateral affected kidney and the contralateral unaffected one, any metabolic features unique to the environment of the calyceal diverticulum could be obscured. A previous study, while somewhat older, demonstrated that separate urine sampling of ipsilateral stone forming kidneys and non-stone forming contralateral kidneys revealed a nearly twofold increase in calcium excretion from the stone forming kidney. [16]

We found that the data from the three patients who underwent direct aspiration of urine from the calyceal diverticula is remarkably similar; the urine aspirated directly from the diverticulum contains the lowest SSCaOx when compared to the ipsilateral and contralateral renal pelves. This cannot be definitively explained, but speculative scenarios may conclude that the low SSCaOx in the calyceal diverticula is due to reabsorption of ions across the urothelium, consumption of ions through their incorporation into the stone, or possibly some combination thereof. That calcium oxalate stone formation occurs in the milieu of low SSCaOx implies a role for other factors such as stasis.

Conclusions

The relative contribution of metabolic factors versus stasis in the pathogenesis of stone formation in calyceal diverticula has historically been an unsettled issue. The work presented herein represents one of the largest populations of patients with calyceal diverticular calculi to undergo complete metabolic characterization. Patients with calyceal diverticular calculi have urine calcium excretion that is similar to that of common calcium oxalate stone formers, and indeed their SS CaOx values are equivalent as well. These data suggest a metabolic component to the pathogenesis of calyceal diverticular stones. However, the data obtained by direct aspiration shows that the SS CaOx is lower, suggesting that urinary stasis also promotes stone formation.

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