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Characterization of Inner Medullary Collecting Duct Plug Formation among Idiopathic Calcium Oxalate Stone Formers

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Abstract

Objective—To study the prevalence of, risk factors for, and renal functional consequences of ductal plug formation in idiopathic CaOx stone formers were determined.

Patients and Methods—Accessible renal papillae were videotaped to determine the percent surface area (SA) occupied by plaque and ductal plug in a consecutive cohort of iCaOx SF undergoing percutaneous nephrolithotomy for stone removal.

Results—Between 2009 and 2014 iCaOx SF comprised 96 of 240 enrolled patients. Of these, 41 (43%) had ductal plugs. Mean plaque surface area did not differ between the low and high % plug groups (2.1% vs 3.4%, respectively). The amounts of mean % SA plaque and ductal plug were not strongly correlated (spearman's $\rho=0.12$, $p=0.3$). Patients with $>1\%$ mean SA plug had a higher urinary pH (median 6.5 vs 6.0, $p=0.02$) and elevated urinary hydroxyapatite supersaturation (median 5.4 vs 3.7 D.G.; $p=0.04$). Those with $>1\%$ plugging had more extensive ductal dilation ($p=0.002$) compared to those with $\leq 1\%$. However, estimated glomerular filtration rate (eGFR) was the same (median 75.4 versus 74.7 ml/min/1.73m²). Number of prior stone events was associated with mean and maximum papillary surface area occupied by plug ($p<0.05$ for both), but not plaque ($p=0.3$ and $p=.5$, respectively).

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Conclusion—Within a cohort of iCaOx SF, macroscopic plaque and ductal plugs often coexist. Intraluminal features known to favor calcium phosphate crystallization appear to play a role in plug formation. The pathogenic significance of these plugs remains to be established, although their extent appears to correlate with stone burden.

Keywords

Calcium Oxalate; Nephrolithiasis

Objectives

In 1937, Alexander Randall was the first to conclude the existence of a calcium plaque deposited in the renal papillae and observed renal calculi attached to these plaques.(1) Since then, investigations have demonstrated the apatite composition of Randall's plaque, its formation within the medullary interstitium, and the relationship of plaque surface area corresponding to severity of disease.(2, 3) (4) Nearly 80 years since this discovery, significant advances in the understanding and treatment of calcium oxalate (CaOx) stone disease have been made; however, much is still unknown regarding calculogenesis in CaOx stone formation.

Idiopathic CaOx (iCaOx) stone formers (SF), the most common group in the United States, are defined as individuals with predominantly CaOx stones without any systemic disease as a cause of stone formation such as inflammatory bowel disease, prior bowel resection, pancreatic malabsorption, renal tubular acidosis, primary hyperoxaluria, hyperparathyroidism, Dent's disease, medullary sponge disease, or sarcoidosis.(5) Investigations into stone formation in individuals with systemic disease as a cause of CaOx stone formation, in particular small bowel disease, have discovered evidence of cellular injury and inflammation associated with stone formation, Randall's plaque, and duct of Bellini deposits of apatite. (6) Interestingly, previous studies on iCaOx SF failed to demonstrate evidence of ductal deposits or cellular injury, with only predominant overgrowth of stone on plaque. (7–9)

It has been proposed that two distinct cellular histopathologic phenotypes exist between calcium SF: Randall's plaque and ductal plugs.(3, 6, 7) However, recent investigation of a random consecutive cohort of iCaOx SF have demonstrated ductal plugging in iCaOx SF without evidence of underlying systemic disease, and frequently co-existing with Randall's plaque.(9) Ductal plugging is proposed to arise from tubular injury and altered inner medullary collecting duct or duct of Bellini loss of acidification with concurrent rise in local urinary pH as well as calcium phosphate supersaturation and crystallization.(6, 10) A recent report also described renal papillary pathology and potential renal functional consequences of papillary ductal plugging among hydroxyapatite (HA) SF.(10) Thus, in the current study we evaluated the presence of, risk factors for, and renal functional consequences of ductal plug formation among an ongoing consecutive cohort of iCaOx SF with detailed clinical history, papillary mapping data and histology, and structural and compositional stone analysis.

Patients and Methods

This study was approved by the Mayo Clinic Institutional IRB. Since September 2009 we have prospectively enrolled patients undergoing percutaneous nephrolithotomy (PCNL) in a prospective cohort. All non-pregnant patients over the age of 18 years undergoing elective PCNL for symptomatic upper tract urinary stone disease were informed of our study and offered enrollment. For the current study, the 240 patients enrolled as of December 2014 were evaluated. CT images were available before the procedure to assess current stone burden. Twenty four hour urine studies are obtained with patients on a random diet and performed 6 weeks after stone removal. Percutaneous access was placed in either an upper or lower pole posterior renal calyx to maximize stone removal. One fragment of the removed stone was sent for culture and the remaining for detailed structural and compositional analysis by micro-CT and directed infrared spectroscopy as previously described.(11) The majority of the removed stone material analyzed by microCT was used to define the overall stone composition breakdown.

Patients were classified as idiopathic CaOx SF (iCaOx SF) if their stones lacked brushite (BR), struvite, uric acid (UA) or drug components and contained >50% CaOx monohydrate, CaOx dihydrate, or a combination of the two. Those with any clinical history consistent with systemic disease as a cause for CaOx stone disease including malabsorption from bariatric weight loss surgery, small bowel resection, inflammatory bowel disease, or pancreatic disease; renal tubular acidosis; primary hyperoxaluria; or hyperparathyroidism were excluded from the study. A total of 96 of the 240 patients met these criteria as iCaOx SF.

After all stone material was removed, the internal papillary structures of the kidney were systematically evaluated and videotaped using a flexible digital nephroscope as previously described.(12) The location of each papilla was determined using fluoroscopy with instillation of contrast through the nephroscope. The collected video data was then used to digitally quantify the percent surface area covered by plaque and ductal plug (Figure 1). Representative still images of each papilla were captured from the video footage. All videos and images were reviewed to determine the location and distribution of the papillae, plaque, and plugs. By using video editing software, the area of the papillae, individual plaques, and plugs were outlined to calculate the percent surface area of the plaque and plug. Once the entire kidney was mapped, a papillary tip biopsy was taken endoscopically from an accessible, representative calyx which best illustrated renal pathology. The calyx was selected based on the ability to provide the best biopsy specimen within the confines of the surgical access and instruments. All biopsies were then inspected and characterized by a dedicated renal pathologist (LPH). A duct of Bellini plug was defined as a crystalline structure protruding from a duct of Bellini that could be physically removed, and a plaque was defined as the presence of discolored and slightly raised urothelium consistent with subepithelial crystal deposition that could not be removed. Assessment of ductal dilation and papillary flattening was performed by a single surgeon (AEK) to decrease variability in ductal and papillary assessment intraoperatively. Ductal dilation was quantified as mild, moderate or severe as follows (Figure 2): mild ductal dilation comprised minimal dilation of a duct of Bellini as small as a pinpoint hole; moderate dilation comprised dilation of a duct to at least 1 mm in size or multiple small pinpoint dilations covering less than half the

surface area of the papillae; severe dilation comprised dilation of a duct > 1 mm or multiple smaller dilations covering greater than half the surface area of the papillum. Papillary flattening, an indicator of parenchymal change from stone disease and/or obstruction, was similarly quantified as follows: mild papillary flattening comprised minimal papillary architecture change from normal; moderate was defined as significant but not complete flattening of the papilla; severe papillary flattening was defined as complete destruction of the papilla with loss of a normal contour.

Univariate analyses were performed using Kruskal-Wallis, Wilcoxon rank sum, chi-squared and Fisher's exact tests. Multivariate analyses were performed using linear regression. All reported p-values were two-sided, with $p < 0.05$ considered to be statistically significant. Statistical analyses were performed using SAS software, version 9.3 (SAS Institute, www.sas.com).

Results

A total of 96 iCaOx formers were studied, of whom 41 (43%) demonstrated any ductal plugs. Utilizing a cutpoint for significant ductal plugging, defined as >1% (as previously described (9, 12)), 16 (17%) of these patients were found to have significant ductal plugging (supplemental figure 1). Group demographics including age, gender, and diagnosis of diabetes, HTN, CKD, stone burden, and history of prior stone surgery were similar between iCaOx SF who had >1% ductal plugging and those who did not (Table 1). Furthermore, there were no significant differences in mean plaque surface area, maximum plaque surface area, or secondary stone composition between those with <1% versus >1% ductal plugging (Table 2). The amounts of mean % SA plaque and ductal plug were not strongly correlated (spearman's $\rho=0.12$, $p=0.3$). Out of the 96 patients, 45 (47%) had no plugging and <5% mean plaque SA. Number of prior stone events was associated with mean and maximum papillary surface area occupied by plug, but not plaque (supplementary table 1).

Compared to those with 1% ductal plugging, those with >1% ductal plugging had more extensive ductal dilation (median total dilated duct score 1.0 vs. 4.0 ; $p=0.002$), but a similar degree of total papillary flattening (median 0.0 vs. 0.5; $p=0.3$). However, estimated glomerular filtration rate (eGFR) was similar in those with < 1% (median 75.4 ml/min/1.73m²) versus > 1% (74.7 ml/min/1.73m²) ductal plugging ($p=0.6$).

Patients with a higher mean percentage SA ductal plugging were more likely to have a higher urinary pH (median 6.5 vs 6.0, $p=0.02$) (supplementary table 2) and elevated urinary HA SS (median 5.4 vs 3.7 DG; $p=0.04$). Conversely, and because of the higher pH, UA SS was lower in those with higher amounts of ductal plug (median -2.3 vs 0.8 DG, $p=0.02$; supplementary table 2). A total of 75% of those with high % SA ductal plug were female compared to only 51% in the low SA group ($p=0.08$).

Using stepwise selection, statistical models were created to predict ductal plug formation. After adjusting for secondary stone composition (pure CaOx versus secondary HA), urine pH and HA SS were the only variables found to be significantly associated with mean % SA

ductal plugging when fitted using separate models ($p=0.033$ and $p=0.043$, respectively, see supplementary table 3).

Discussion

In this study we analyzed a consecutive cohort of 96 patients with a clinical diagnosis of iCaOx stone formation and demonstrated that both Randall's plaque and duct of Bellini plugging were commonly observed. In particular ductal plugging was found in 43% of iCaOx SF. A greater % SA of ductal plugging was associated with a higher urinary pH and HA SS. These results suggest that intraluminal features known to favor calcium phosphate stone formation, namely higher urinary pH, may play a role in the formation of ductal plugging in iCaOx SF.

Numerous studies have evaluated the role of Randall's plaque formation in calcium stone formation, in particular that of iCaOx SF.(2–4, 13–15) However, ductal plug formation in patients with iCaOx stone disease has not been as well described, and its prevalence and significance in this the group of iCaOx patients remains ill-defined. Evan and colleagues (3) utilized infrared and x-ray diffraction as well as electron and light microscopy and confirmed observations made by Alexander Randall nearly 70 years prior: plaques were located in the interstitium, composed of HA, and were often observed in selected patients with iCaOx SF. Hypercalciuria was a prominent feature of the iCaOx SF studied by Evan and colleagues. Randall's plaque was also observed in control (non-SF) kidneys, but to a lesser extent than the iCaOx SF. Conversely, no evidence of HA within ducts of Bellini was provided.(3) The Evans group concluded that the basement membrane of the loop of Henle served as the origin of Randall's plaque, perhaps due to the unusually thick collagen matrix of the membrane that creates an ionic attraction for calcium and phosphate. This same report contained papillary biopsies of CaOx SF with bowel disease, specifically intestinal bypass, and demonstrated that they did not contain significant amounts of plaque but instead intratubular crystal deposits within the collecting ducts.

In our current study, we focused on a cross section of patients presenting to a tertiary care center for surgical management of their stone disease. In contrast to prior studies which focused exclusively on hypercalciuric iCaOx SF, we found in our cross sectional cohort of iCaOx SF that over 40% demonstrated ductal plugs, with and without plaque (Figure 2). Importantly the current group of iCaOx SF lacked secondary causes (e.g., malabsorption, hyperparathyroidism, renal tubular acidosis) but were not markedly hypercalciuric (mean 24 hr calcium excretion 209 mg). Furthermore, our cohort tended to demonstrate a higher 24hr urine volume, lower excretions of sodium, and uric acid, and a higher urinary pH, than those reported by Evan and colleagues. More recent studies from Evan and colleagues have documented ductal plugging in BR and HA SF, and those CaOx SF with a history of bowel resection, ileostomy and/or gastric bypass.(6, 7) However, our current cohort of iCaOx SF is the largest one to describe the relative prevalence of both Randall's plaque and ductal plugs in a cross sectional cohort of iCaOx SF with perhaps more diverse underlying metabolic risk factors.

The amount of endoscopic ductal plugging and Randall's plaque were not significantly correlated raising the question whether other mechanisms of stone initiation might be present in a subset of what clinically appear as iCaOx SF. In addition, those with a greater burden of stone disease, as reflected by number of total lifetime stone events had a greater amount of plugs, but not plaque. These intriguing findings require further research. For example, it's possible that a more overtly hypercalciuric cohort might have a greater amount of plug, and this might correlate with stone burden, as has previously been reported. Overall, the results do suggest there may be multiple anatomic calcifications within the kidney that correlate with stone burden, and provide complimentary indications of disease burden.

Certain characteristics of the current study cohort deserve emphasis. The majority of patients in the current study with ductal plugs were female, and of those with > 1% ductal plugging 12 of 16 were female. Ductal plug formers (>1%) had a higher urinary pH as well as HA SS and lower UA crystal supersaturation. Prior investigations by Park and colleagues(16) have observed a female predominance among HA SF as well as those with collecting duct plugging, presumably associated with HA SS within the ducts. Indeed, it is well established that HA stone formation is significantly related to urinary pH.(16)

Based upon current classification schemes SF with up to 50% HA are considered iCaOx SF. (9) Thus, it is not surprising that certain iCaOx SF might have urinary conditions that favor HA crystallization. Further, these are the same urine features (especially higher urinary pH), that we found associated with ductal plug. A recent study by Evan and colleagues described the histopathology of a cohort of BR and HA SF.(10) Ten of the eleven HA stones contained CaOx (mean ($\pm$ SD) $26\pm 17\%$). In this report the HA SF as a group had evidence for papillary changes and functional CKD that was more pronounced than the BR SF. Thus, it might not be surprising if patients with mixed CaOx stones that were majority CaOx also had some degree of papillary duct plugging and perhaps pathophysiological consequences. However, in our study eGFR was not associated with the degree of ductal plugging (Table 2).

Furthermore, while ductal dilation was statistically greater among those with >1% ductal plugging, the amount of papillary flattening overall was not (Table 2). Thus, while our study does provide evidence for some papillary pathological consequence of ductal plugging, they appear more subtle than those described by Evan and colleagues SF.(10) It is possible that these anatomic changes could have an impact on GFR over a longer period of time or in a subset of more severely affected individuals, although our study does not provide strong evidence to support this hypothesis at this time. To answer these questions, careful clinical study or additional broad cohorts of iCaOx SF with papillary data will be required.

Recent investigation has also aimed to explain histopathologic differences between groups of SF. Evan and colleagues investigated histopathologic differences in patients identified as iCaOx, BR, and HA SFs. Patients were placed into one of these three groups of SF on the basis of author defined arbitrary cut-offs that iCaOx SFs do not form duct of Bellini deposits and BR and HA SFs do. What was observed in each of these groups is intriguing and may point to more of a continuum in the progression of certain SFs to calcium phosphate stone formation, collecting duct plugging and cellular injury. The authors observed differences between BR and HA SFs, having a significantly elevated pH when compared with iCaOx SF, 6.3 vs 6.0 ($p=0.05$) respectively. Differences in urinary calcium and calcium phosphate

SS were also significantly elevated in HA and BR groups when compared to iCaOx SF. On micro-CT analysis they observed stone growth on Randall's plaque in >50% of HA SFs, all iCaOx SF and in 12% of BR SF. Ductal plugging was observed in only HA and BR stone formation. Our group of iCaOx SFs with >1% ductal plugs appear similar to the HA group of Evan and colleagues(10) in manifesting a higher urinary pH, which begs the question: are certain iCaOx SF (and also HA SF) more likely to form ductal plugs due to a higher urinary pH, closely resembling that of HA SFs? What are the underlying reasons for this slightly elevated pH? Is it acquired over time, perhaps in response to accumulated damage from stones, crystals or ductal plugs? Or are other environmental or genetic factors to blame. Further investigation into the differences and similarities of these two groups of SF is required.

Limitations to the study include its observational design and relatively small sample size (96 patients). Our institution is a tertiary referral center and may represent significant bias in terms of generalizability of our patient population. Further studies are needed to address the significance of collecting duct plugging and their role in pathogenesis of iCaOx SF.

Conclusion

Within a cohort of iCaOx SFs, plaque and ductal plugs often coexist. Those with greater amounts of ductal plugging also tended to have higher levels of urinary pH, HA SS and lower UA SS, and also trended towards being female. Intraluminal features known to favor calcium phosphate namely higher pH, may play a role in ductal plug formation. However, the pathogenic significance of these ductal plugs in the iCaOx population remains to be established.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Upper pole (UP 2 and UP 1) and mid-pole (MP 1) calyx from 3 iCaOx patients. Ductal plugs are marked with the arrow and plaque encircled.

Figure 2.
Examples of mild (UP1) and severe (MP1) ductal dilation

Table 1

Patient Demographics

	IMCD plug 1% IMCD plug Surface (N=80)	IMCD plug >1%IMCD plug Surface(N=16)	P
Age, median(IQR)	61.9 (56.8, 68.7)	65.9 (58.4, 70.3)	0.5
Female, %y	41 (51.3%)	12 (75.0%)	0.08
BMI, median(IQR)	29.1 (25.4, 33.4)	29.9 (26.5, 32.6)	0.5
Diabetes, %y	20 (25.0%)	2 (12.5%)	0.3
Hypertension, %y	37 (46.3%)	7 (43.8%)	0.9
CKD, %y	1 (1.3%)	0 (0.0%)	0.7
Number of stones, median(IQR)	1.0 (0.0, 3.5)	2.5 (0.5, 4.0)	0.3
eGFR	75.4 (63.6, 91.0)	74.7 (61.5, 86.9)	0.6

Table 2

Stone composition, mapping and histopathologic analysis

<i>Mapping Characteristics</i>	IMCD plug 1% Surface IMCD plug (N=80)	IMCD plug >1%Surface IMCD plug (N=16)	P
Plaque % Surface (median, IQR)	2.1 (1.0, 4.3)	3.4 (0.9, 7.2)	0.6
Plaque % Maximum Surface (median, IQR)	4.8 (1.8, 9.2)	6.7 (1.9, 12.2)	0.6
Dilated ducts, %y	50 (62.5%)	14 (87.5%)	0.05
Maximum Severity Dilated Ducts, n(%)			0.002
None	30 (37.5%)	2 (12.5%)	
Mild	32 (40.0%)	4 (25.0%)	
Moderate	9 (11.3%)	3 (18.8%)	
Severe	9 (11.3%)	7 (43.8%)	
Total Dilated Ducts Score (median, IQR)	1.0 (0.0, 2.0)	4.0 (2.0, 6.0)	0.002
Papillary flattening, %y	28 (35.0%)	8 (50.0%)	0.3
Maximum Degree Papillary Flattening, n(%)			0.4
None	52 (65.0%)	8 (50.0%)	
Mild	14 (17.5%)	5 (31.3%)	
Moderate	6 (7.5%)	2 (12.5%)	
Severe	8 (10.0%)	1 (6.3%)	
Total Papillary Flattening Score (median, IQR)	0.0 (0.0, 2.0)	0.5 (0.0, 2.5)	0.3
<i>Stone Composition Characteristics</i>			
Pure CaOx, %y	40 (50.0%)	8 (50.0%)	1.0
% HA (median, IQR)	6.5 (1.0, 15.5)	9.0 (2.5, 20.0)	0.6
<i>Biopsy data</i>			
Intraluminal crystals, %y	39 (79.6%)	8 (100.0%)	0.3
Interstitial inflammation %y	47 (95.9%)	7 (87.5%)	0.4
Punctate Basement membrane staining, %y	25 (51.0%)	6 (75.0%)	0.3
Polarizing crystals, %y	3 (6.1%)	1 (12.5%)	0.5
Dense staining surrounding basement membranes, %y	25 (51.0%)	5 (62.5%)	0.7