Intra-tubular deposits, urine and stone composition are divergent in patients with ileostomy

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Patients with ileostomy typically have recurrent renal stones and produce scanty, acidic, sodium-poor urine because of abnormally large enteric losses of water and sodium bicarbonate. Here we used a combination of intra-operative digital photography and biopsy of the renal papilla and cortex to measure changes associated with stone formation in seven patients with ileostomy. Papillary deformity was present in four patients and was associated with decreased estimated glomerular filtration rates. All patients had interstitial apatite plaque, as predicted from their generally acid, low-volume urine. Two patients had stones attached to plaque; however, all patients had crystal deposits that plugged the ducts of Bellini and inner medullary collecting ducts (IMCDs). Despite acid urine, all crystal deposits contained apatite, and five patients had deposits of sodium and ammonium acid urates. Stones were either uric acid or calcium oxalate as predicted by supersaturation, however, there was a general lack of supersaturation for calcium phosphate as brushite, sodium, or ammonium acid urate because of the overall low urine pH. This suggests that local tubular pH exceeds that of bulk urine. Despite low urine pH, patients with an ileostomy resemble those with obesity bypass, in whom IMCD apatite crystal plugs are found. They are, however, unlike these bypass patients in having interstitial apatite plaque. IMCD plugging with sodium and ammonium acid urate has not been found previously and appears to correlate with formation of uric acid stones.

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Patients with ileostomy typically produce a scanty, acidic, sodium-poor urine because of abnormally large enteric losses of water and sodium alkali.[1–3] As a result, they often develop calcium oxalate (CaOx) and/or uric acid kidney stones, although their urine calcium, uric acid, and oxalate excretions are not themselves remarkably high.[4] Sometimes, renal function may decline because of renal uric acid crystallizations, presumably when increased enteric fluid losses reduce urine volume and pH; this is referred to as acute uric acid nephropathy.[5,6] To date, nothing has been published regarding renal papillary tissue in patients with ileostomy and recurrent renal stones; we present here our findings on seven such patients.

These patients present an opportunity to test some mechanisms suggested by our previous studies. The common idiopathic CaOx stone former, who has no systemic disease apart from familial (idiopathic) hypercalciuria, deposits apatite plaque in the renal papillary interstitium, and stones grow on papillary surfaces attached to sites of sub-urothelial plaque.[7,8] Interstitial apatite plaque abundance is proportional to urine calcium excretion, and inverse to urine pH and volume;[9] hence, we might expect such plaque in ileostomy patients even in the absence of hypercalciuria. Patients with high urine volumes and pH, such as brushite stone formers[10] and those with renal tubular acidosis,[11] do not develop plaque, although they are hypercalciuric. Neither do patients with obesity bypass and enteric hyperoxaluria;[7] the latter have low urine pH but high urine volumes and low urine calcium. Ileostomy or colostomy lower both urine volume and pH thus plaque might occur, despite the lack of hypercalciuria in these patients.

We have regularly found intra-tubular deposits of apatite in patients who develop phosphate stones,[10–12] not an unexpected outcome given that such patients produce an alkaline urine supersaturated with respect to phosphate phases. Cystinuria also leads to such deposits,[13] which are found in tubules that are plugged with cystine. Perhaps such local obstruction reduces local acidification leading to an increase in calcium phosphate supersaturation; alkali

treatment for prevention of cystine stones could also be a factor. Hyperparathyroid stone disease produces both interstitial plaque and intra-tubular deposits,[12] which are reasonable given sustained and severe hypercalciuria, which would foster plaque, and a higher than usual urine pH, which would foster tubule deposits. However, obesity bypass patients present an anomaly in having tubule apatite deposits with an acid urine pH, in which intra-tubular apatite would not be a stable phase.[7,14] For them, we have been forced to postulate local tubular loss of acidification as we did for cystinuria.

In ileostomy or colostomy, we would expect interstitial apatite plaque from low urine volume and pH, and uric acid deposits in collecting ducts—because of low urine and collecting duct fluid pH. In particular, we would not expect apatite deposits to develop within collecting ducts, because tubule fluid must have a low pH that corresponds to the low pH of the final urine; low pH would not support apatite formation. Therefore, in addition to presenting the tissue and clinical results, we are interested in testing these two reasonable predictions in order to clarify mechanisms for plaque and tubule deposits.

RESULTS

Patients

Seven patients (three females) were studied (Table 1). All had undergone ileostomy and total colectomy for ulcerative colitis (five patients), Crohn's disease (patient 2), and cancer (patient 5). Stones were either CaOx or uric acid, and in one subject (patient 6) both were formed. Age at ileostomy ranged from 10 to 58 years, and the interval from ileostomy to our study ranged from 3 to 41 years. Rates of procedures varied from none to as many as 14, the present biopsy not included.

Surgical anatomy and renal function

All seven patients displayed both white (interstitial apatite) plaque (Figure 1a, c, and d, Table 2), and yellow (intra-tubular crystal) plaque, which was not further quantified (Figure 1a–d). The amounts of white plaque varied widely (percentage of mean papillary surface area, Table 2). The percentage of abnormal papillae varied among the patients from 0 to 25% (papillary deformity, Table 2). Some papillae with flattening and retraction also showed dilation of the mouths of ducts of Bellini (BD) (Figure 1d), but dilation and retraction were not well correlated (Table 2, Figure 1b and c).

Large crystal deposits were seen beneath the urothelium filling tubular lumens (Figure 2a). Crystals occasionally protrude from dilated BD openings (Figure 2b). On some papillae in two patients (Table 2), CaOx stones were attached to the papillary surface (Figure 2c) and at sites of white

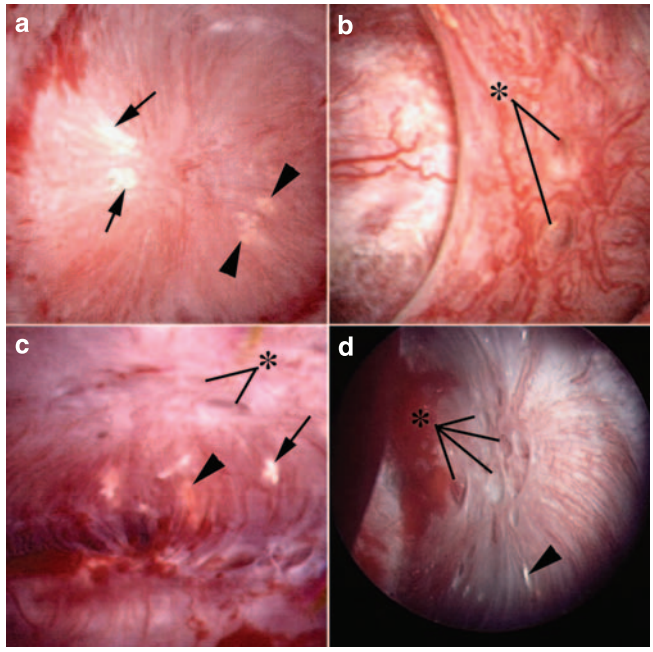

Figure 1 | Endoscopic images of papilla from ileostomy patients with kidney stones. Papillary morphology of ileostomy patients ranged from a normal conical shape (**a**–**c**) to flattened and retracted (**d**). Dilated openings (asterisks) to ducts of Bellini were common in both the normal and deformed papillae (**b**–**d**). Variable amounts of white (arrows) and yellow (arrowheads) plaque were seen separately (**d**) or on the same papilla (**a** and **c**).

Table 1 | Clinical characteristics and serum chemistries

Patient no.	Sex	Age at colectomy (years)	Age at first stone (years)	Prior stones	Age at biopsy (years)	ESWL	PNL	Total procedures	Serum creatinine (mg/dl)	Serum CO_2 (mM/l)	Serum K (mM/l)	eGFR (ml/min)
1	F	21	31	>12/2	53	2/2	1/1	6/6	0.9	23	4.5	70
2	M	10	27	3/1	43	1/1	1/1	5/3	1.2	25	3.4	70
3	F	19	25	10/3	58	3/0	3/2	9/3	1	29	4.7	61
4	F	20	60	2	61	1	2	5	0.8	26	4.3	78[†]
5	M	58	59	8/6	61	1/0	2/1	5/2	2.3	19	5.2	31[†]
6	M	36	49	7/7	63	6/6	1/1	15/15	1.3	28	3.8	63
7	M	49	51	1	51	0	1/1	1/1	0.9	26	3.6	108

eGFR, estimated glomerular filtration rate; ESWL, extracorporeal shock wave lithotripsy; F, female; M, male; MDRD, Modification of Diet in Renal Disease; PNL, percutaneous nephrolithotomy.
Prior stones: number of stones/number in the PNL kidney; total procedures: number procedures/procedures in the PNL kidney, including cystoscopy, open surgery, ureteroscopy, as well as ESWL and PNL.
Patient 4 had a history of scleroderma, and patients 6 and 7 had diabetes. eGFR using MDRD equation.
[†]Patients with a previous history of acute renal failure.