Acute Phosphate Nephropathy following Oral Sodium Phosphate Bowel Purgative: An Underrecognized Cause of Chronic Renal Failure

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The findings of diffuse tubular injury with abundant tubular calcium phosphate deposits on renal biopsy are referred to as nephrocalcinosis, a condition typically associated with hypercalcemia. During the period from 2000 to 2004, 31 cases of nephrocalcinosis were identified among the 7349 native renal biopsies processed at Columbia University. Among the 31 patients, 21 presented with acute renal failure (ARF), were normocalcemic, and had a history of recent colonoscopy preceded by bowel cleansing with oral sodium phosphate solution (OSPS) or Visicol. Because the precipitant was OSPS rather than hypercalcemia, these cases are best termed *acute phosphate nephropathy*. The cohort of 21 patients with APhN was predominantly female (81.0%) and white (81.0%), with a mean age of 64.0 yr. Sixteen of the 21 patients had a history of hypertension, 14 (87.5%) of whom were receiving an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. The mean baseline serum creatinine was 1.0 mg/dl, available within 4 mo of colonoscopy in 19 (90.5%) patients. Patients presented with ARF and a mean creatinine of 3.9 mg/dl at a median of 1 mo after colonoscopy. In a few patients, ARF was discovered within 3 d of colonoscopy, at which time hyperphosphatemia was documented. Patients had minimal proteinuria, normocalcemia, and bland urinary sediment. At follow-up (mean 16.7 mo), four patients had gone on to require permanent hemodialysis. The remaining 17 patients all have developed chronic renal insufficiency (mean serum creatinine, 2.4 mg/dl). Acute phosphate nephropathy is an underrecognized cause of acute and chronic renal failure. Potential etiologic factors include inadequate hydration (while receiving OSPS), increased patient age, a history of hypertension, and concurrent use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.

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Renal parenchymal calcium deposits usually contain one of two anions, phosphate or oxalate. The two anions can be differentiated in renal biopsies by their different pathologic properties: The birefringence of calcium oxalate under polarized light and the histochemical reaction of calcium phosphate with the von Kossa stain. Nephrocalcinosis denotes a clinical-pathologic entity characterized histologically by abundant renal parenchymal deposits of calcium phosphate associated with chronic tubulointerstitial injury. Clinically, patients with nephrocalcinosis have renal insufficiency, typically of gradual onset, and low-grade proteinuria, usually <1 g/d. Nephrocalcinosis can usually be linked to conditions associated with hypercalcemia, including hyperparathyroidism, states of increased bone turnover, excess intake of vitamin D or calcium, hypercalcemia of malignancy, sarcoidosis, and distal renal tubular acidosis. Only rare reports have focused on phosphate intake as a precipitant for nephrocalcinosis, such as in the setting of phosphate treatment for hypophosphatemic rickets (1).

We recently reported five cases of renal failure and "acute nephrocalcinosis" after bowel cleansing with oral sodium phosphate solution (OSPS; Phospho-soda, CB Fleet, Lynchburg, VA) (2). The five patients had normal baseline renal function and presented with acute renal failure (ARF) and a mean creatinine of 4.9 mg/dl at 3 d to 2 mo (mean 3 wk) after colonoscopy. In all five patients, renal biopsy revealed acute nephrocalcinosis with abundant distal tubular calcium phosphate deposits. At 4 mo after colonoscopy, renal function was unchanged in four patients and mildly improved in one patient.

This report enlarges our experience to 21 cases that were diagnosed at our center, with emphasis on potential risk factors and outcome. The longer follow-up and larger cohort of patients has the advantage of allowing us to define better the condition's natural history and potential reversibility. On the basis of the critical pathogenetic role for exogenous oral phosphate intake, we believe that the term *acute phosphate nephropathy* (3) more aptly describes this entity than our previous usage of *acute nephrocalcinosis*. Our biopsy incidence of acute phosphate nephropathy over the past 5 yr exceeds that of other forms of nephrocalcinosis, indicating the emerging importance of this clinical-pathologic entity and the need for improved recognition.

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Materials and Methods

All renal biopsies that were received at Columbia University Medical Center during the 5-yr period from January 2000 to December 2004 were reviewed for the presence of acute phosphate nephropathy. Diagnostic criteria included (*1*) acute renal failure; (*2*) pathologic findings of acute and/or chronic tubular injury with abundant tubular calcium phosphate deposition; (*3*) recent exposure to an oral sodium phosphate bowel purgative, including Fleet Phosphosoda, a generic equivalent, or Visicol (InKline Pharmaceutical Co., Inc., Blue Bell, PA), a tablet form of identical composition available only by prescription; and (*4*) the absence of hypercalcemia.

Standard processing of renal biopsies included light microscopy, immunofluorescence, and electron microscopy. For light microscopy, all cases were stained with hematoxylin and eosin, periodic acid-Schiff, Masson's trichrome, and Jones methenamine silver. All cases were examined under polarized light and stained with von Kossa to differentiate calcium phosphate (nonpolarizable, von Kossa positive) from calcium oxalate (polarizable, von Kossa negative). For immunofluorescence, 3-μm cryostat sections were stained with polyclonal FITC-conjugated antibodies to IgG, IgM, IgA, C3, C1q, kappa, lambda, fibrinogen, and albumin (Dako Corp., Carpinteria, CA). Electron microscopy was performed using a JEOL 100s electron microscope.

Patients' charts were reviewed for age, gender, race, medical history, medications, bowel purgative used for colonoscopy preparation, serum electrolytes, and changes in renal function before and after colonoscopy. ARF was defined as a newly identified doubling of serum creatinine. The single exception is patient 19, who experienced an acute rise in serum creatinine from 1.7 to 2.6 mg/dl but did not achieve a doubling of serum creatinine.

Results

Thirty-one cases of ARF with histologic findings of acute and/or chronic tubular injury and abundant calcium phosphate deposits were identified retrospectively from the archives of the Columbia University Renal Pathology Laboratory between 2000 and 2004. During this period, our laboratory processed a total of 7349 native renal biopsies. Renal allograft biopsies were not considered because of the high incidence of tubular calcium phosphate deposition, hyperparathyroidism, and hypercalciuria in this patient population. Four patients had acute phosphate nephropathy after use of OSPS (before colonoscopy) but were excluded from this report because of the presence of additional (superimposed) renal biopsy findings that could account for the patients' renal failure, including allergic interstitial nephritis, acute postinfectious glomerulonephritis, hepatitis C virus–associated proliferative and crescentic glomerulonephritis, and severe hypertensive arterionephrosclerosis. Two patients were excluded because there was no history of colonoscopy, and two others were excluded because of a known history of unexplained hypercalcemia (one of whom had a recent colonoscopy). Finally, two patients developed acute phosphate nephropathy after colonoscopy but were excluded because neither the physician nor the patient could identify the type of bowel preparation that had been used (3 yr before). The remaining 21 patients met entry criteria for the diagnosis of "acute phosphate nephropathy following oral sodium phosphate bowel purgative" and are the subject of this report. This represents a biopsy incidence of 21 of 7349, or 0.29%. Among the 31 biopsies with findings of acute nephrocalcinosis, it is notable that 25 had recent colonoscopy preceded by OSPS and that two more had recent colonoscopy without record of the bowel preparation administered. Thus, a minimum of 25 (80.6%) of the 31 patients with histologic findings of nephrocalcinosis had a recent history of OSPS use.

With the exception of patient 19 who received Visicol tablets, all of the patients received OSPS, including Fleet Phospho-Soda or a generic equivalent. A single patient received 120 ml of OSPS and a 133-ml sodium phosphate enema over 24 h; this OSPS load significantly exceeded the recommended dose of 3 oz (90 ml) in two divided doses separated by 12 h. The remaining 19 patients received OSPS at the standard dose. Importantly, patients 1 through 5 were the subject of a previous report (2) but are included to provide additional follow-up.

The 21 patients with acute phosphate nephropathy after oral sodium phosphate bowel preparation underwent renal biopsy at 18 different hospitals located in New Jersey (nine patients), New York (six patients), Indiana (three patients), Pennsylvania (one patient), Connecticut (one patient), and Georgia (one patient). Nineteen of the biopsies were received for initial processing and evaluation at Columbia University Medical Center, and two were received for second opinion consultation. All 21 renal biopsies were processed for light microscopy and immunofluorescence; in 19 of 21 cases, tissue was also available for electron microscopy.

The cohort of patients with acute phosphate nephropathy consisted of 17 women and four men, with a mean age of 64.0 yr (range 39 to 82; Table 1). Eighteen patients were 51 yr or older, and 13 patients were 62 yr or older. The majority of patients were white (17 of 21; 81.0%) and had a history of hypertension (16 of 21; 76.2%). Fourteen (87.5%) of the 16 patients with hypertension were treated with either an angiotensin-converting enzyme inhibitor (ACE-I; 7 patients) or an angiotensin receptor blocker (ARB; 7 patients). A history of diabetes, degenerative joint disease, or coronary artery disease was present in 4, 4, and 3 patients, respectively. Patient 1 had a history of mild hyperparathyroidism (with a baseline normal serum calcium), and patient 13 had a history of mild pulmonary sarcoid (no baseline serum calcium available). None of the remaining 19 patients had a history of hypercalcemia or any condition known to cause hypercalcemia (including active malignancy, sarcoidosis, vitamin D intoxication, or milk alkali syndrome). Patients' medications included a lipid-lowering agent, diuretic, or nonsteroidal anti-inflammatory drug (NSAID) in five, four, and three patients, respectively.

Patients with acute phosphate nephropathy had a mean baseline serum creatinine of 1.0 mg/dl (range, 0.6 to 1.7 mg/dl; Table 2). Of note, four (19.0%) of the 21 patients had mild baseline renal insufficiency, with a serum creatinine >1.2 mg/dl. In 19 of the 21 patients, the baseline serum creatinine determination was obtained ≤ 4 mo before colonoscopy, and in 11 patients, the most recent baseline creatinine was ≤ 1 mo before. Patients presented with ARF and a mean serum creatinine of 3.9 mg/dl (range, 1.8 to 6.7 mg/dl) at a median of 1 mo after colonoscopy. The interval between colonoscopy and initial discovery of ARF was ≤ 2 wk in eight (38.1%) of the 21 patients, ≤ 1 mo in 12 (57.1%) patients, and ≤ 2 mo in 18 (85.7%) patients.

Table 1. Demographics and clinical findings in patients with ARF after treatment with OSPS bowel purgative[a]

Patient	Age	Race	Gender	HTN	Diabetes	Medications				Laboratory Parameters at Presentation		
						ACE-I	ARB	Diuretic	NSAID	24-H Urine Protein	Serum Calcium[b] (mg/dl)	Serum Phosphorus[b] (mg/dl)
1	69	W	M	Y	N		Y			412 mg	9.1	5.6
2	82	B	M	Y	N					1+	8.8	4.6
3	55	H	F	Y	Y		Y	Y		92 mg	9.5	4.0, 4.6[c]
4	64	B	F	Y	Y	Y		Y		1.2 g	10.3	NA
5	76	W	F	Y	N		Y			Trace	8.6	6.6 (day 3)
6	53	W	M	Y	N		Y			120 mg	9	2.6
7	81	W	F	N	N					600 mg	8.5	4.3
8	82	W	F	Y	N		Y	Y		123 mg	9.2	4.1
9	57	W	F	Y	N	Y				Trace	9.1	10.2 (day 3)
10	76	W	F	Y	N		Y			472 mg	8.7	4.5
11	74	W	F	Y	N		Y			200 mg	9	NA
12	57	W	F	N	N					140 mg	8.8	6.7 (day 2)
13	43	B	F	Y	Y	Y		Y	Y	130 mg	NA	NA
14	39	W	F	N	N					Negative	8.5	4.3
15	69	W	F	Y	N	Y				500 mg	9.7	4.1
16	66	W	F	Y	Y	Y				Negative	9.4	3.2
17	51	W	F	Y	N				Y	197 mg	9.1	3.5
18	79	W	F	N	N					Trace	9.1	NA
19	44	W	M	Y	N	Y			Y	95 mg	9.2	NA
20	62	W	F	N	N					250 mg	9.4	4.6
21	64	W	F	Y	N	Y				Negative	10.2	4.4

[a]ARF, acute renal failure; OSPS, oral sodium phosphate solution; W, white; B, black; H, Hispanic; M, male; F, female; HTN, hypertension; Y, yes; N, no; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAID, nonsteroidal anti-inflammatory drug; NA, not available.
[b]Normal range for serum calcium 8.4 to 10.3 mg/dl; for serum phosphorus 2.5 to 4.5 mg/dl.
[c]On two separate determinations.

Acute phosphate nephropathy is accompanied by low-grade proteinuria (Table 1). With the exception of patient 4, who had mild nodular diabetic glomerulosclerosis (and a 24-h urine protein of 1.2 g/d), the mean 24-h urine protein was 256 mg/d and the 24-h urine protein was ≤600 mg/d in all 13 patients in whom quantification was available. In the remaining seven patients, urinalysis revealed trace protein (three patients) or 1+ protein (one patient) or was negative for protein (three patients). In all 20 patients with available data, the serum calcium level at the time of discovery of ARF was within the normal range. Serum phosphorus determination at the time of discovery of ARF or at nephrologic evaluation was available in 16 patients, seven of whom had evidence of hyperphosphatemia. This included a phosphorus of 10.2 mg/dl at day 3 after colonoscopy in patient 9, 6.7 mg/dl at day 2 in patient 12, and 6.6 mg/dl at day 3 in patient 5. Thirteen (61.9%) of the 21 patients had a bland urine sediment, while an increase in urinary red blood cells or white blood cells was seen in three and five patients, respectively. Cellular casts were not reported for any patient.

Renal biopsy was performed at a mean of 3.8 mo and a median of 4 mo after colonoscopy, at which time the patients had a mean serum creatinine of 3.7 mg/dl (range, 2.2 to 8.0 mg/dl). During the interval between initial discovery of ARF and renal biopsy, the majority of patients had relatively stable renal function, as evidenced by the minimal decline in mean serum creatinine from 3.9 to 3.7 mg/dl.

Postbiopsy clinical follow-up was available for all patients, with a mean follow-up of 16.7 mo. Four patients went on to develop ESRD that required renal replacement therapy; one of the four patients subsequently underwent successful renal transplantation. Among the remaining 17 patients, 16 (94.1%) have had an improvement in renal function. Among these 17 patients, the mean serum creatinine at the end of the available follow-up period was 2.4 mg/dl (range, 1.3 to 3.4 mg/dl). Although the improvement in renal function is noteworthy, only four patients have reached a serum creatinine <2.0 mg/dl and no patient has returned to baseline.

The renal biopsy findings in patients with acute phosphate nephropathy are highlighted in Table 3. Sampling for light microscopy included a mean of 22.8 glomeruli (range, 6 to 53 glomeruli), and a mean of 3.2 (14.0%) glomeruli were globally sclerotic. In 20 of 21 cases, glomeruli appeared histologically unremarkable. In the single remaining case (patient 4), glomeruli exhibited evidence of mild nodular diabetic glomerulosclerosis.

Table 2. Serum creatinine changes in patients with ARF after treatment with OSPS bowel purgative[a]

Patient	Baseline Creatinine (mg/dl)	Interval Pre-CSPY	Creatinine upon Discovery of ARF (mg/dl)	Interval Post-CSPY	Creatinine at Time of Renal Biopsy (mg/dl)	Interval Post-CSPY	Final Creatinine (mg/dl)	Interval Post-CSPY
1	1.2	2 wk	6.7	1 mo	6.3	7 wk	ESRD	18 mo
2	0.9	1 d	5.2	1 wk	4.9	4 wk	ESRD	9 mo
3	0.6	3.5 mo	4.5	13 d	4	4 mo	2.7	24 mo
4	0.9	4 mo	2.3	2 mo	3	7 mo	ESRD	15 mo
5	0.9	12 mo	6	3 d	8	6 d	1.9	20 mo
6	1	1 d	4.8	12 d	2.2	3 mo	1.3	55 mo
7	0.9	1 mo	3.3	4.5 mo	3.3	5 mo	2.6	15 mo
8	1.1	3.5 mo	4.4	3 wk	3.3	13 mo	3.1	15 mo
9	0.7	1 d	1.8	1 d	3.1	3 wk	2.7	2 mo
10	0.9	4 mo	3.8	2 mo	3.6	6 mo	2.1	33 mo
11	1.5	2 mo	3.9	1 mo	3	4 mo	3	5 mo
12	1	1 d	3.8	2 d	3.1	14 d	1.5	2 mo
13	0.9	2 wk	2.2	2 mo	2.3	6 mo	1.8	13 mo
14	0.7	11 d	4.5	5 d	4.1	17 d	2.7	11 mo
15	1.3	1 mo	4.2	5 mo	4.6	7 mo	ESRD	13 mo
16	1.4	8 yr	3.7	19 d	3.9	4 mo	3.4	11 mo
17	0.9	2 wk	3	5 wk	2.7	2 mo	2.1	13 mo
18	0.7	3 mo	3.4	3 mo	3.2	4 mo	2.8	6 mo
19	1.7	2 wk	2.6	2 mo	2.3	5 mo	2.2	9 mo
20	0.9	7 wk	5.9	8 d	3.6	17 d	3.4	23 mo
21	0.9	2 mo	2.6	2 mo	2.3	4 mo	1.8	38 mo

[a]CSPY, colonoscopy.

The predominant light microscopic finding in all cases was tubular injury, often accompanied by tubular atrophy and interstitial fibrosis. The acute tubular degenerative changes involved all tubular segments from proximal to distal to collecting duct and included epithelial simplification, luminal ectasia, loss of proximal tubular brush border, enlarged reparative nuclei with prominent nucleoli, shedding of cellular fragments into the tubular lumina, and dropout of tubular epithelial cells. The tubular injury was accompanied by interstitial edema. In four patients, the acute tubular degenerative changes were not accompanied by significant tubular atrophy and interstitial fibrosis. These four patients had the shortest interval from colonoscopy to renal biopsy (≤17 d), and, in light of the absence of time for the development of tubulointerstitial scarring, the pattern of histologic injury most closely resembled changes seen in acute tubular necrosis.

In the majority of biopsies, the acute tubular degenerative changes were accompanied by evidence of chronic, irreversible tubular injury in the form of tubular atrophy and interstitial fibrosis. This pattern of injury was referred to as an acute and chronic tubulointerstitial nephropathy and resembled changes seen in repeat biopsies from patients with acute tubular necrosis that does not clinically resolve. Among the 17 patients with histologic findings of acute and chronic tubulointerstitial nephropathy, tubular atrophy and interstitial fibrosis involved a mean of 47.1% of the cortical area sampled (range 15 to 70%). All 17 patients had evidence of ongoing tubular injury, which ranged from mild and localized (13 patients) to diffuse (4 patients). Interstitial inflammation was graded as minimal or mild in 16 patients and moderate in five; none of the patients had significant tubulitis. Consistent with the age of the patients, vascular disease was noted in all but one case and ranged from mild (4 cases) to moderate (13 cases) to severe (3 cases).

The most distinctive finding in all cases of acute phosphate nephropathy was abundant calcium phosphate deposits in distal tubules and collecting ducts (Figure 1). The calcifications formed basophilic, rounded concretions and typically were present in >40 tubular profiles per biopsy. The calcifications were located within the cytoplasm of tubular epithelial cells, within tubular lumina, and less prominently within the interstitium. The calcifications stained intensely with the von Kossa stain and did not polarize, confirming their composition as calcium phosphate. Calcium phosphate deposits were clustered in straight segments, suggesting a distribution in medullary rays. Although the calcifications predominated in the renal cortex, medullary calcifications were also identified.

Ultrastructural evaluation revealed diffuse tubular degenerative changes, including loss of brush border, cytoplasmic attenuation, decreased organelle content, loss of intercellular contacts, dilation of the endoplasmic reticulum, and shedding of cytoplasmic fragments into the tubular lumen. The calcifications appeared as electron-dense spicules or crystals that were radially oriented around a central nidus. Similar to light microscopy, the calcifications had an intratubular, intracytoplasmic, and interstitial distribution. A single patient exhibited segmental small subepithelial electron-dense deposits, consis-

Table 3. Renal biopsy findings in patients with ARF after treatment with OSPS bowel purgative[a]

Patient	No. of Glomeruli	No. of Sclerotic Glomeruli	Tubular Injury	Tubular Calcium Phosphate	% TA and IF	Interstitial Inflammation	Vascular Disease	Histopathologic Pattern
1	53	5	Diffuse	Diffuse	30%	Mild	Moderate	A/C TIN
2	30	15	Diffuse	Diffuse	40%	Mild	Moderate	A/C TIN
3	47	4	Diffuse	Diffuse	60%	Minimal	Moderate	A/C TIN
4[b]	6	1	Mild	Diffuse	50%	Moderate	Moderate	A/C TIN, NDGS
5	22	2	Diffuse	Diffuse	None	Minimal	None	ATN
6	19	1	Mild	Diffuse	25%	Mild	Mild	A/C TIN
7	20	2	Mild	Diffuse	60%	Moderate	Severe	A/C TIN
8	32	9	Mild	Diffuse	60%	Mild	Severe	A/C TIN
9	17	2	Diffuse	Diffuse	30%	Moderate	Moderate	A/C TIN
10[c]	9	1	Mild	Diffuse	60%	Moderate	Severe	A/C TIN, segmental MG
11	16	1	Mild	Diffuse	50%	Minimal	Moderate	A/C TIN
12	16	2	Diffuse	Diffuse	10%	Mild	Moderate	ATN
13	17	2	Mild	Diffuse	60%	Mild	Moderate	A/C TIN
14	32	2	Diffuse	Diffuse	5%	Minimal	Mild	ATN
15	17	6	Mild	Diffuse	70%	Mild	Moderate	A/C TIN
16	19	4	Mild	Diffuse	70%	Moderate	Moderate	A/C TIN
17	13	2	Mild	Diffuse	40%	Mild	Moderate	A/C TIN
18	17	1	Mild	Diffuse	20%	Minimal	Moderate	A/C TIN
19	20	3	Mild	Diffuse	15%	Minimal	Mild	A/C TIN
20	16	1	Diffuse	Diffuse	None	Minimal	Mild	ATN
21	40	2	Mild	Diffuse	60%	Mild	Moderate	A/C TIN

[a]TA and IF tubular atrophy and interstitial fibrosis; A/C TIN, acute and chronic tubulointerstitial nephropathy; NDGS, nodular diabetic glomerulosclerosis; ATN, acute tubular necrosis; NA, not available; MG, membranous glomerulopathy.
[b]Patient 4 also had biopsy findings of mild nodular diabetic glomerulosclerosis.
[c]Patient 10 also had biopsy findings of rare segmental subepithelial deposits, seen only by electron microscopy, consistent with segmental MG.

tent with segmental changes of membranous glomerulopathy (patient 10). In light of the lack of demonstrable positivity by immunofluorescence, the 24-h urine protein of only 472 mg/d, the finding of only 20% foot process effacement, and the presence of only segmental membranous changes, membranous glomerulopathy did not seem to be contributing significantly to the patient's ARF. With the exception of the patient with mild diabetic glomerulosclerosis (patient 4), ultrastructural evaluation revealed ≤20% foot process effacement in 17 of 18 patients. Immunofluorescence was performed on all 21 cases and exhibited no evidence of positivity for immune reactants in the glomerular or tubulointerstitial compartments.

In our previous report on acute nephrocalcinosis, lectin and immunohistochemical staining showed that the calcium phosphate deposits were confined to distal tubules and collecting ducts (2). Immunohistochemical staining also revealed a marked increase in tubular cellular proliferation (as evidenced by staining for Ki-67) and diminished staining for and apical translocation of Na^+,K^+-ATPase.

Discussion

OSPS is an over-the-counter purgative that is used for bowel cleansing before colonoscopy. The recommended bowel-cleansing regimen consists of two 45-ml doses taken 12 h apart, the night before and the morning of colonoscopy. Each 45-ml bottle contains 18.8 g of monobasic sodium phosphate and 4.3 g of dibasic sodium phosphate. Because only a small volume of OSPS is required, ample fluid intake is strongly encouraged (32 oz of clear liquid with each 45-ml dose).

OSPS has been in widespread use as a bowel purgative before colonoscopy since approximately 1990. Compared with polyethylene glycol–based lavage solution, the minimal volume of oral intake required with OSPS is associated with less patient discomfort, greater compliance, and improved colonic cleansing (4). Serum electrolyte monitoring over the initial 24 h after administration of OSPS reveals small, statistically significant, but rapidly reversible increases in phosphorus, sodium, chloride, hematocrit, and serum osmolality (4). OSPS is generally regarded as a safe agent but is contraindicated in patients with kidney disease and should be used with caution in patients with electrolyte disturbances.

Transient hyperphosphatemia is seen in patients who receive OSPS. One study that included 54 patients found a mean increase in serum phosphorus of 4.1 mg/dl after the second 45-ml administration (4); serum calcium levels were available in only seven patients and were minimally affected, falling from a

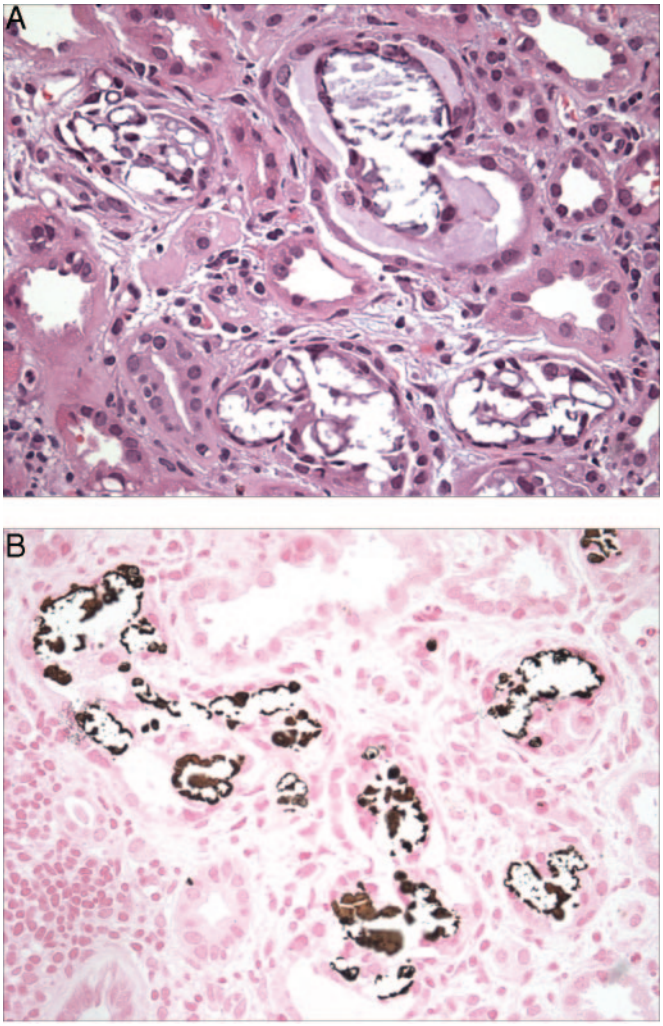

Figure 1. Histologic findings in acute phosphate nephropathy. (A) Basophilic, rounded calcium phosphate deposits are present within the cytoplasm of tubular epithelial cells and within tubular lumina (hematoxylin and eosin). (B) The calcifications stain intensely with the von Kossa stain, confirming their composition as calcium phosphate. Magnification, ×400.

mean to 10.1 to 9.9 mg/dl. A single patient reached a serum phosphorus level of 11.6 mg/dl (4). A larger study examined electrolyte changes in 143 patients who received OSPS and found a mean increase in serum phosphorus of 3 mg/dl and a mean decline in serum calcium of 0.3 mg/dl (5). A more recent study found that older patients achieve greater levels of hyperphosphatemia after use of OSPS (6). In particular, the mean increase in serum phosphorus after use of OSPS was 3.4 mg/dl in patients who were between 25 and 35 yr of age, compared with 5.5 mg/dl in individuals who were older than 56 yr (6).

Reports of ARF after use of OSPS can be found in the literature. A 76-yr-old man who received excessive doses of OSPS developed oliguric ARF with a peak phosphorus level of 15.8 mg/dl (7). After acute hemodialysis, serum phosphorus rapidly declined and renal function returned to normal 1 mo later. A 77-yr-old woman received a single 45-ml dose of OSPS and developed ARF with a creatinine of 5 mg/dl, a calcium of 4.6 mg/dl, and a serum phosphorus of 27.8 mg/dl (8). After treatment with intravenous fluid, calcium carbonate, and aluminum hydroxide, her creatinine declined to 2.5 mg/dl and serum calcium and phosphorus levels normalized. Neither patient underwent renal biopsy. There have been six previous reports of biopsy-documented acute phosphate nephropathy after use of OSPS, including a 71-yr-old woman (3) and the first five patients in this study, who were the subject of a previous publication (2).

In the absence of discovery of ARF immediately after colonoscopy and in the setting of significant hyperphosphatemia, the causative role of OSPS in the development of acute phosphate nephropathy is likely to be overlooked. In our experience, ARF was discovered within 1 wk of colonoscopy in only five of the 21 cases of acute phosphate nephropathy, and only three had significant hyperphosphatemia (phosphorus $>$ 6 mg/dl) at the time of presentation (patients 5, 9, and 12). As a result, the diagnosis of acute phosphate nephropathy was unsuspected by the majority of treating nephrologists.

The true incidence of acute phosphate nephropathy cannot be determined, although this entity is likely to be widely underrecognized. A typical hypothetical case is that of a 70-yr-old woman who has a history of hypertension and presents to her internist for her annual physical examination and is found to have a creatinine of 3 mg/dl. After referral to a nephrologist, she is noted to have stable, nonprogressive renal insufficiency, minimal proteinuria, and inactive urinary sediment. Serologic and imaging studies are unrevealing. The patient is followed for some time, and the creatinine trends minimally downward. This clinical scenario is one in which most nephrologists would not recommend renal biopsy (9). In the minority of patients who undergo renal biopsy, the findings of nephrocalcinosis will suggest the possibility of conditions associated with hypercalcemia. Few nephrologists would inquire about recent colonoscopy or use of OSPS, causing the association to be overlooked. For patients who schedule colonoscopy after their annual physical and develop asymptomatic renal insufficiency, the rise in serum creatinine may go undetected until the next annual physical examination.

There are multiple lines of evidence that strongly point to OSPS as the causative agent in acute phosphate nephropathy. First and foremost is the distinct histologic finding of abundant calcium phosphate crystals in renal tubules. Second is the close temporal relationship between the use of OSPS and the development of ARF. Third is our finding that 25, possibly even 27, of the 31 patients with biopsy findings of nephrocalcinosis had a history of a recent colonoscopy procedure preceded by bowel cleansing with OSPS. Fourth is the observation that exogenous phosphorus administration may lead to nephrocalcinosis in both mice (1,10,11) and children with hypophosphatemic rickets (1). In these children, the histologic findings are similar to those that are the subject of this report (1).

Calcium-phosphate product (CPP) is generally regarded as an indicator of the risk of calcium phosphate precipitation in the kidney. By extrapolation, the normal range for CPP is 21 to 45.9. A mean peak CPP of 71.28 is reached transiently after use of OSPS (5). Unfortunately, the peak CPP level in our cohort is

unknown because these electrolytes are not routinely measured after colonoscopy.

OSPS is widely regarded as a safe agent for bowel cleansing before colonoscopy. Although transient hyperphosphatemia occurs, it is not associated with untoward events in the majority of patients. Factors that may predispose patients to ARF after OSPS include inadequate hydration, increased patient age, hypertension with histologic evidence of arterionephrosclerosis, concurrent treatment with ACE-I or ARB, or inappropriate use of OSPS in patients with chronic kidney disease or electrolyte disorders. Our data underscore the importance of age and co-administration of agents that may reduce renal perfusion. Eighteen (85.7%) of the 21 patients reported were 51 yr or older, and 13 (61.9%) were older than 62 yr. As previously noted, older patients achieve a greater degree of hyperphosphatemia after use of OSPS (6). A total of 76.2% of patients had a history of hypertension, and 87.5% of these were being treated with either an ACE-I or an ARB. Four (19%) patients were receiving diuretics, and three (14%) were on NSAIDs. Five patients were receiving more than one of these agents simultaneously. Because OSPS produces osmotic diarrhea and resultant volume depletion, adequate hydration is likely to be a central issue. ACE-I, ARB, diuretics, and NSAIDs all exacerbate volume depletion, particularly in older patients. With avid proximal tubular sodium and water reabsorption, volume depletion in turn may produce higher intratubular CPP in distal tubules, the site where calcium phosphate precipitation occurs. Murine studies that have demonstrated strain-dependent differences in the development of nephrocalcinosis after administration of oral phosphorus (11) suggest that genetic factors may also play a role in humans. Strategies to prevent the development of acute phosphate nephropathy after OSPS include rigorous attention to adequate hydration and possibly not administering ACE-I, ARB, diuretics, and NSAID on the day before and the day of the colonoscopy procedure. OSPS should be used with great caution in elderly patients.

Of note, 17 (81%) of our 21 cases occurred in women. Whether this represents a true gender predisposition or a chance occurrence would need to be confirmed in larger cohorts. This female predilection raises questions about possible differences in the response of elderly women to acute volume depletion on the basis of their smaller body mass. Other possible predisposing factors include baseline mild renal insufficiency in four (19%) of 21 patients, three of whom had biopsy evidence of significant (at least moderate) arteriosclerosis. It is of interest that all but five of the 21 patients had evidence of moderate or severe arteriosclerosis on renal biopsy. Pre-existing arteriosclerosis of aging or hypertension may predispose to ARF after volume depletion as a result of the higher perfusion pressures required to maintain adequate renal perfusion, analogous to the risk for ARF in older adults with minimal-change disease and pre-existing arteriosclerosis (12). Only two patients had a history of conditions that are potentially associated with hypercalcemia (including one with mild hyperparathyroidism and one with mild pulmonary sarcoid), although serum calcium was normal before colonoscopy in the former and unavailable in the latter.

It is interesting to note that patient 19 received Visicol, rather than OSPS, before the development of ARF and acute phosphate nephropathy (13). Visicol is a newer purgative preparation that has a near identical composition to OSPS. Unlike OSPS, Visicol is available in a pill form. Because the pill form is tasteless, with resultant potential for abuse, Visicol is available only by prescription. Visicol is associated with a similar degree of transient hyperphosphatemia as OSPS.

At the time of our initial report, it was unclear how reversible the acute phosphate nephropathy would be over the long term. The larger experience reported here indicates a high risk for chronic renal failure. Although patients presented with mean serum creatinine of 3.9 mg/dl at a median of 1 mo after colonoscopy, only four (19%) patients progressed to ESRD at 9 to 18 mo (mean, 13.8 mo) after colonoscopy. All but one of the remaining 17 (94%) patients had a subsequent improvement in renal function (mean serum creatinine, 2.4 mg/dl at the end of the follow-up period); however, all were left with some degree of renal insufficiency, and none returned to their baseline creatinine levels. Our mean follow-up period was 16.7 mo, and longer follow-up is needed to determine whether there is potential for any further improvement in renal function.

In summary, OSPS is an effective bowel purgative for use before colonoscopy. Although transient hyperphosphatemia occurs, ARF is a seemingly rare but underrecognized complication. Potential contributing factors include inadequate hydration; increased patient age; history of hypertension and arteriosclerosis; and concurrent use of ACE-I, ARB, diuretics, or NSAIDs. Although renal function may improve, all (100%) patients in this report were left with chronic renal insufficiency and 19% developed ESRD, underscoring the importance of acute phosphate nephropathy as a cause of chronic irreversible renal injury. Our findings strongly suggest the need for further study and possibly revised guidelines to address the use of OSPS in older patients who have a history of hypertension and are receiving ACE-I, ARB, diuretics, or NSAIDs. Furthermore, OSPS should be avoided in patients with chronic kidney disease. Given the remarkably high incidence of acute phosphate nephropathy (80.6%) among native renal biopsies with findings of nephrocalcinosis at a single large center over the past 5 yr, we believe that this entity is underrecognized. Greater awareness of this entity among nephrologists, gastroenterologists, primary care physicians, and renal pathologists is needed to define better the incidence and potential risk factors for this adverse event.

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