AJKD

Kidney Biopsy Teaching Case

Hypophosphatemia in Kidney Transplant Recipients: Report of Acute Phosphate Nephropathy as a Complication of Therapy

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Hypophosphatemia is a common complication after kidney transplant, affecting >90% of patients. However, no specific recommendations for phosphate repletion exist for transplant recipients. We report a case of a 70-year-old highly sensitized woman with end-stage renal disease caused by diabetic nephropathy who underwent deceased donor kidney transplant. Four weeks later, she was noted to have hypophosphatemia with undetectable serum phosphate levels, and she reported mild diarrhea. She was started on oral phosphate supplementation. On a routine visit 2 weeks later, she was found to have an acute increase in serum creatinine level and kidney biopsy was performed. We discuss the causes, management, and complications of hypophosphatemia in kidney transplant.

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INDEX WORD: Acute kidney injury; hyperparathyroidism; hypophosphatemia; kidney transplant; phosphate.

INTRODUCTION

Hypophosphatemia is a common complication in kidney transplant recipients in the first year after transplant.[1-4] Complications of severe hypophosphatemia are broad and include confusion, weakness, myocardial dysfunction, and rhabdomyolysis. There are no specific guidelines for phosphate repletion in the kidney transplant population. We report a case of hypophosphatemia after kidney transplant complicated by kidney failure.

CASE REPORT

Clinical History and Initial Laboratory Data

A 70-year-old woman with end-stage renal disease from diabetic nephropathy underwent deceased donor kidney transplant in April 2009. Medical history included hypertension, ischemic colitis, and atrial fibrillation. She had been on hemodialysis therapy for 7 years, and laboratory study results before transplant included the following values: calcium, 9 mg/dL (2.24 mmol/L); phosphate, 3.9 mg/dL (1.25 mmol/L); 25-hydroxyvitamin D, 35 ng/mL (87.36 nmol/L); and parathyroid hormone (PTH), 279 pg/mL (279 ng/L). She was receiving paricalcitol with every hemodialysis session in addition to sevelamer hydrochloride for phosphate control.

The patient was highly sensitized, with a pretransplant panel-reactive antibody titer of 91%, and the donor was a 39-year-old woman who died of anoxic brain injury after trauma. She received thymoglobulin for induction therapy, followed by tacrolimus, azathioprine, and prednisone for maintenance immunosuppression. She also was started on treatment with calcitriol, 0.25 μg/d, and calcium carbonate, 1,250 mg, twice daily (500 mg of elemental calcium) upon transplant. The immediate posttransplant period was remarkable for delayed transplant function requiring 2 hemodialysis sessions for management of hyperkalemia. A biopsy at 1 week after transplant showed acute tubular injury with focal tubular necrosis without evidence of rejection. Four weeks after transplant, serum creatinine level reached a nadir of 1.16 mg/dL (102.54 μmol/L), with estimated glomerular filtration rate (GFR) of 46 mL/min/1.73 m^2 (0.77 mL/s/1.73 m^2; calculated using the isotope-dilution mass spectrometry–traceable 4-variable MDRD [Modification of Diet in Renal Disease] Study equation). At that time, she was noted to have hypercalcemia (calcium, 10.4 mg/dL [2.59 mmol/L]) and serum phosphate level less than assay detection (<1 mg/dL [<0.32 mmol/L]). The patient was concerned about mild diarrhea, but did not report weakness, confusion, irritability, or paresthesia. She was started on treatment with potassium phosphate oral supplementation (K-Phos Original, Beach Pharmaceuticals), 500 mg, 3 times a day.

On a routine visit 2 weeks later, the patient was found to have a serum creatinine level increase to 3.86 mg/dL (341 μmol/L), and she reported worsening diarrhea. Medications included tacrolimus, azathioprine, prednisone, aspirin, simvastatin, felodipine, glyburide, metoprolol, omeprazole, trimethoprim-sulfamethoxazole, valganciclovir, calcium carbonate, calcitriol, and potassium phosphate. Physical examination showed blood pressure of 118/66 mm Hg, heart rate of 78 beats/min, and clear oropharynx with dry mucosa. Jugular veins were not distended. The abdomen was soft and nontender with increased bowel sounds, and lower extremities showed no edema. Muscular strength was preserved, and no sensory deficits were detected.

The patient was admitted for hydration and possible repeated kidney biopsy due to high concern of rejection in this highly

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Table 1. Laboratory Parameters on Admission

Parameter	Value	Reference Range
Serum sodium (mEq/L)	136	136-145
Serum potassium (mEq/L)	4.2	3.4-5
Serum chloride (mEq/L)	110	98-107
Serum bicarbonate (mEq/L)	29	22-31
Serum glucose (mg/dL)	130	70-100
Serum urea nitrogen (mg/dL)	36	6-23
Serum creatinine (mg/dL)	3.86	0.5-1.2
Serum calcium (mg/dL)	6.6	8.8-10.5
Ionized calcium (mmol/L)	0.8	1.13-1.32
Serum albumin (g/dL)	3.8	3.7-5.4
Serum phosphate (mg/dL)	5.3	2.4-5
25-Hydroxyvitamin D (ng/mL)	32	25-80
PTH (pg/mL)	515	15-65
Urine pH	7.5	4.5-8
Hematocrit (%)	30	36-48
Tacrolimus (ng/mL)	10.5	5-10
Creatine kinase (U/L)	28	27-218

Note: Conversion factors for units: serum creatinine in mg/dL to μmol/L, $\times$88.4; serum urea nitrogen in mg/dL to mmol/L, $\times$0.357; serum glucose in mg/dL to mmol/L, $\times$0.055; serum calcium in mg/dL to mmol/L, $\times$0.2495; serum albumin in g/dL to g/L, $\times$10; serum phosphate in mg/dL to mmol/L, $\times$0.3229; 25-hydroxyvitamin D in ng/mL to nmol/L, $\times$2.496. No conversion necessary for serum sodium, potassium, chloride and bicarbonate in mEq/L and mmol/L and PTH in pg/mL and ng/L.

Abbreviation: PTH, parathyroid hormone.

sensitized patient. Results of additional laboratory studies on admission are listed in Table 1. Kidney ultrasound showed mild increased echogenicity with normal renal perfusion throughout and increased resistive index at 1.0. Creatinine level did not improve after administration of intravenous normal saline solution, and kidney biopsy was performed.

Kidney Biopsy

The kidney transplant biopsy specimen contained 18 glomeruli and consisted of both cortex and medulla. Glomeruli with global sclerosis were not seen. The sample showed focal irregularities in the height of proximal tubule cells, slight distention of the lumen, focal vacuolization of the cytoplasm, and moderate protein reabsorption granules. Several distal tubules showed extensive damage to the cells and prominent calcium deposition (Fig 1A). The deposited crystals were reactive for phosphate using von Kossa stain (Fig 1B) and were positive for calcium using alizarin red stain (Fig 1C). Intraluminal calcifications were located predominantly in the distal segment of tubules in the outer medulla and cortex. Calcification type was dystrophic in nature, which is seen commonly in the setting of cellular injury or necrosis. There was no deposition along tubular basement membranes as seen in metastatic calcifications in the setting of hypercalcemic states. The biopsy specimen showed no evidence of acute rejection or significant chronic changes. Staining for C4d was negative in peritubular capillaries using immunofluorescence microscopy.

Diagnosis

Acute phosphate nephropathy secondary to oral phosphate supplementation.

Clinical Follow-up

The patient was started on treatment with calcium acetate, 1,334 mg, with meals for phosphate binding in association with a phosphate-restricted diet. Phosphate levels trended down and creatinine level slowly improved in combination with an increase in calcium levels (Fig 2). One week later, calcium acetate treatment was suspended after phosphate levels reached the reference range, and her diet was normalized to normal phosphate content. In the subsequent few months, she became hypercalcemic (calcium, 10.5-11.6 mg/dL [2.62-2.89 mmol/L]), phosphate levels ranged from 1.6-2.4 mg/dL (0.52-0.78 mmol/L), and PTH levels slowly

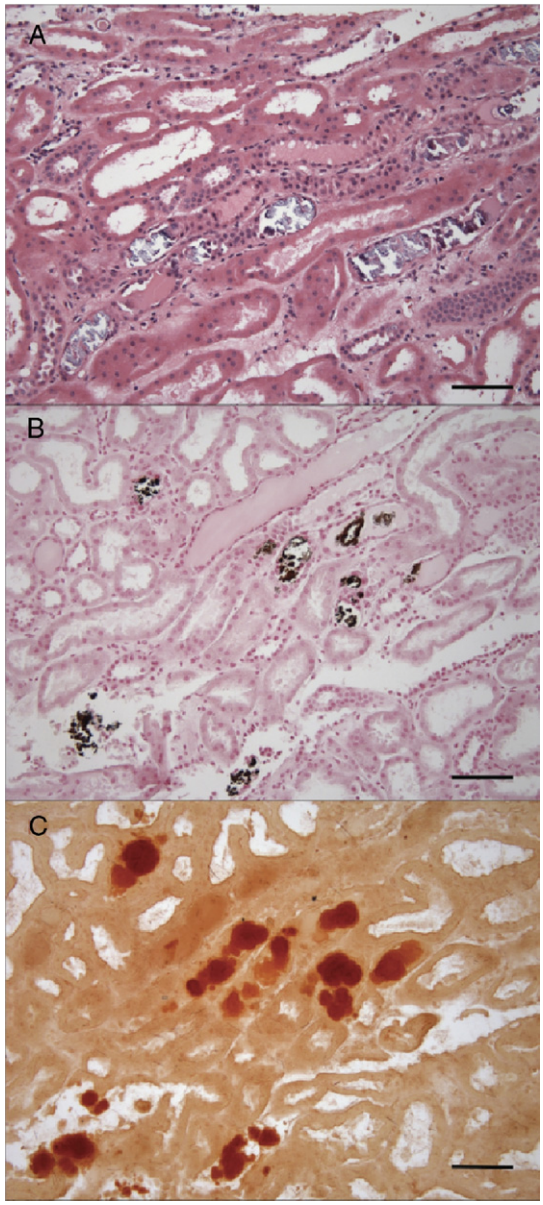

Figure 1. Light microscopy of the kidney biopsy specimen (bars, 100 μm). (A) Hematoxylin and eosin stain shows irregular intraluminal deposits of basophilic crystalline material within tubules of the outer medulla. (B) Using von Kossa histochemical stain, phosphate within crystals is shown by chemical substitution of the calcium for silver, resulting in dark-staining metallic silver grains. (C) Calcium within the crystalline material forms a lacquer when sections are exposed to alizarin red.

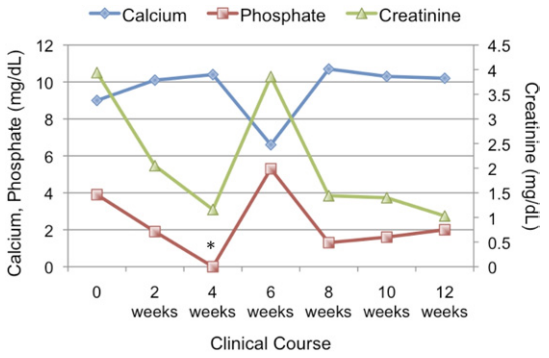

Figure 2. Trend of serum calcium, phosphate, and creatinine levels after transplant. Time zero defined as day of kidney transplant. Oral phosphate supplementation was started at week 4 after transplant (*). Conversion factors for units: serum creatinine in mg/dL to μmol/L, $\times$88.4; serum calcium in mg/dL to mmol/L, $\times$0.2495; serum phosphate in mg/dL to mmol/L, $\times$0.3229.

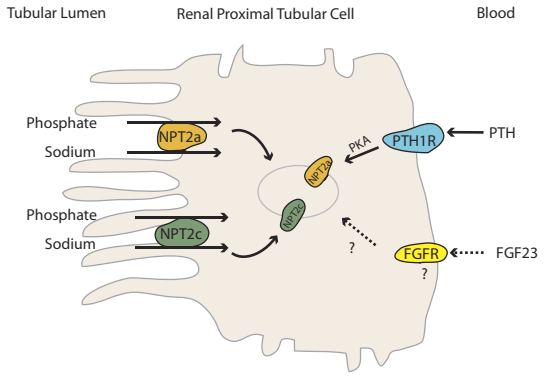

Figure 3. Effects of parathyroid hormone (PTH) and FGF-23 (fibroblast growth factor 23) on renal phosphate handling. PTH is produced by the parathyroid gland and secreted into the circulation. In proximal tubular cells, PTH interacts with the type 1 PTH receptor (PTH1R) and through protein kinase A (PKA) and protein kinase C (not shown) stimulates the internalization and degradation of sodium-phosphate cotransporters (NPT2a and 2c). FGF-23 is produced in bone and also decreases the expression of these NPT2 cotransporters. However, the mechanism involved in FGF-23 signaling is unknown. Abbreviation: FGFR, fibroblast growth factor receptor.

decreased (from 156 to 98.5 pg/mL [156 to 98.5 ng/L]). Calcitriol and calcium supplementation had to be suspended because of hypercalcemia. Urinary fractional excretion of phosphate was increased at 42%. The low phosphate level was managed conservatively, and the patient reported the absence of neurologic or musculoskeletal symptoms. Serum creatinine level reached a nadir of 1.2 mg/dL (106 μmol/L) with estimated GFR of 43 mL/min/1.73 m^2 (0.72 mL/s/1.73 m^2) 4 months after transplant.

DISCUSSION

Hypophosphatemia is a common complication after kidney transplant, affecting >90% of patients.[1-4] In general, hypophosphatemia can occur by 1 or more of 3 primary mechanisms: (1) inadequate intestinal phosphate absorption, (2) excessive renal phosphate excretion, or (3) rapid redistribution of phosphate from the extracellular fluid into bone or soft tissue.[5]

Patients after kidney transplant show inappropriately increased urinary excretion of phosphate, evidenced by increased fractional excretion of phosphate.[4,6] It is believed that the mechanism of posttransplant hypophosphatemia is related to a disorder in regulation of tubular reabsorption of phosphate as a consequence of increased PTH level and activity, increased levels of FGF-23 (fibroblast growth factor 23), and side effects from immunosuppressive drugs (Table 2).

Tubular phosphate transport is mediated by sodium-phosphate cotransporters (NPT2a and NPT2c; encoded by the *SLC34A1* and *SLC34A3* genes, respectively) that colocalize in the apical brush border membrane of the proximal tubule.[7] Their expression is regulated by PTH and FGF-23, which decrease the number of sodium-phosphate cotransporters from the apical membrane[8-11] by rapid internalization and subsequent degradation of these receptors (Fig 3).[7] Most kidney transplant recipients usually have a combination of increased FGF-23 and PTH levels at the time of transplant, which most likely act synergistically to increase phosphate wasting in this population (Table 2).[3,4,6] FGF-23 also inhibits PTH synthesis and 1α-hydroxylase, which leads to a decrease in the activated form of vitamin D. This in turn is important for phosphate absorption in the gastrointestinal tract.[12] FGF-23 level has been identified as the best predictor of serum phosphate level nadir after kidney transplant.[3,4,6]

Of immunosuppressive drugs, tacrolimus has been linked to a marked decrease in NPT2a cotransporter

Table 2. Risk Factors for Hypophosphatemia in Kidney Transplant Recipients Early After Transplant

Factors	Effects	Consequences
↑ PTH	↓ NPT2a and 2c cotransporters on proximal tubules	↑ Urinary phosphate excretion
↑ FGF-23	↓ NPT2a and 2c cotransporters on proximal tubules; inhibits 1α-hydroxylase vitamin D	↑ Urinary phosphate excretion; ↓ intestinal phosphate absorption
↓ 1,25-vitamin D	↓ NPT2b on intestinal mucosa	↓ Intestinal phosphate absorption
Tacrolimus	↓ NPT2a on proximal tubules	↑ Urinary phosphate excretion
High-dose steroids	↓ NPT2a on proximal tubules	↑ Urinary phosphate excretion

Abbreviations: FGF-23, fibroblast growth factor 23; NPT2, sodium-phosphate cotransporter 2; PTH, parathyroid hormone.

expression in animal models,[13,14] possibly contributing to phosphate wasting in kidney recipients. A similar observation was made for high doses of steroids.[15] However, hypophosphatemia typically does not occur after other solid-organ transplants in which similar immunosuppressive regimens are used. This suggests that immunosuppressive drugs are unlikely to be of primary importance in the development of urinary phosphate wasting, but they may exacerbate tubular dysfunction in combination with the mentioned factors.

In addition, vitamin D deficiency (<25 ng/mL) can decrease intestinal absorption of dietary phosphorus and increase PTH levels, exacerbating hypophosphatemia. Moreover, experimental studies suggest an additional role for 1,25-dihydroxyvitamin D in enhancing renal phosphate reabsorption.[16,17] Interestingly, 25-hydroxyvitamin D levels are usually decreased in the first 3 months posttransplant, requiring special monitoring at this time[6] to prevent a deficit in the substrate for 1α-hydroxylase.

Clinical manifestations of severe hypophosphatemia (phosphate <1.0 mg/dL [<0.32 mmol/L]) reflect a generalized defect in cellular energy metabolism because of adenosine triphosphate depletion, leading to neurologic, cardiovascular, and musculoskeletal manifestations.[5] Neurologic symptoms may include lethargy, confusion, disorientation, paresthesia, seizures, coma, or death. Myocardial contractility may be impaired and diaphragm weakness may affect respiratory status. Finally, muscular manifestations include proximal myopathy, dysphagia, and rhabdomyolysis.

The hypophosphatemia usually regresses spontaneously by 1 year after successful kidney transplant[6]; however, in some patients, it may persist for more than 10 years.[18] The major consequence of persistent renal phosphorus wasting is a progressive decrease in mineral density, which may contribute to the increased risk of fractures in the post–kidney transplant population.[19] FGF-23 levels decrease dramatically in the first 3 months after transplant, but reach concentrations similar to those in creatinine-adjusted controls only at 12 months.[6] Similarly, PTH levels also decrease after transplant. However, they remain higher than those for creatinine-adjusted controls.[6] This presumably is related to parathyroid hyperplasia during end-stage kidney disease, which has a very long involution after transplant.[20]

In the general population, phosphate repletion usually is recommended when phosphate levels are <2 mg/dL (<0.65 mmol/L).[5] The presence of symptomatic complications may warrant more aggressive repletion with intravenous phosphate therapy. However, oral phosphate supplementation has been linked to an increased prevalence of nephrocalcinosis in kidney transplant recipients,[21,22] augmenting the risk up to 6 times in 1 study.[22] Calcium phosphate deposition is seen in ~30% of kidney recipients within the first 6 months after kidney transplant.[21,22] The long-term consequences of nephrocalcinosis are still unknown, but Pinheiro et al[23] reported a 27% decrease in transplant survival in kidneys with nephrocalcinosis in a 12-year follow-up after transplant. This suggests that nephrocalcinosis could be an important risk factor for progressive transplant failure, as has been described for the native kidney.[24]

Nonetheless, acute kidney injury secondary to phosphate deposition in kidney transplants is an uncommon finding.[25] In this case, we believe that multiple factors triggered calcium phosphate deposition, including oral phosphate supplementation (~1,500 mg/d), mild volume depletion from diarrhea, prior tubular injury from ischemia, and inappropriately increased PTH levels. Furthermore, the high tacrolimus level could have decreased GFR through vasoconstriction and possibly increased phosphate wasting by affecting expression of the NPT2 cotransporters. In combination, these factors led to a high urinary phosphate load to a single kidney, which precipitated with calcium in the tubules. There was a concomitant decrease in serum calcium level and increase in creatinine level (Fig 2), which classically has been reported in the older literature to be associated with calcium phosphate deposition and kidney failure.[26] Unfortunately, FGF-23 measurement was not available during admission. However, we would expect a high level, contributing to the described picture. Finally, evaluation of dietary phosphate intake is important and often difficult to determine. Sources of high phosphate content include carbonated beverages[27] and food additives,[28] which can considerably increase daily phosphate intake.

We recommend conservative management of hypophosphatemia in transplant recipients, geared toward increasing phosphate intake through dietary changes. Oral supplementation with potassium phosphate should be used only in patients with persistent severe hypophosphatemia (phosphate <1.0 mg/dL [<0.32 mmol/L]) despite nutritional interventions. Initial dosage should be 1,000 mg/d of oral phosphate, distributed in small doses throughout the day to avoid an acute increase in serum phosphate level. Careful monitoring should be established when oral supplementation is initiated because of the risk of acute phosphate nephropathy, especially because phosphate supplementation can lead to significant diarrhea. Major risk factors for acute phosphate nephropathy include the following: large phosphate load, decreased GFR, older age, volume depletion, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, diuretics, or nonsteroidal anti-inflammatory

drugs.[29] Vitamin D deficiency before transplant also should be addressed if 25-hydroxyvitamin D levels are <30 ng/mL (<74.88 nmol/L). Moreover, it might be prudent to avoid the use of 1,25-dihydroxyvitamin D (calcitriol) early after transplant, especially in patients with delayed transplant function. In a small short-term trial, cinacalcet use in kidney transplant recipients was shown to correct urinary phosphate wasting mainly by controlling PTH levels,[30] suggesting a possible role of this drug in the management of posttransplant hypophosphatemia. However, larger trials with longer follow-up are necessary to elucidate its role.

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