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Case Report

Severe Hypophosphatemia in a Patient with Diabetic Ketoacidosis and Acute Respiratory Failure

Although hypophosphatemia is a common complication during therapy of diabetic ketoacidosis, it is seldom severe and rarely causes clinical manifestations. We report a 39-year-old woman with diabetic ketoacidosis who developed acute respiratory failure after therapy. Although hyperglycemia and acidosis were corrected after treatment, respiratory distress and weakness still persisted. The chest radiograph showed no active lung lesion. Brain CT revealed no significant abnormality. Echocardiographic study revealed normal LV systolic wall motion. Blood biochemistry demonstrated severe hypophosphatemia of 0.3 mg/dL (normal value: 2.5 to 4.5 mg/dL). Phosphate replacement therapy with potassium phosphate was given. The patient's clinical condition improved steadily over the next few days, and after 4 weeks of hospitalization, she was discharged home without obvious long-term sequelae. In a critically ill patient, the symptoms of hypophosphatemia are not apparent and may mimic the symptoms of other underlying disease. Although phosphate replacement is not recommended routinely in diabetic ketoacidosis, if the patient develops cardiopulmonary distress, anemia or severe hypophosphatemia, phosphate therapy under close surveillance is indicated.

Excessive urinary phosphorus excretion in patients with uncontrolled diabetes mellitus has been noted since the nineteenth century.¹ Insulin therapy-induced hypophosphatemia was recognized almost 70 years ago.² Complications of severe hypophosphatemia include weakness, respiratory failure, heart failure, paresthesias, dysarthria, confusion, stupor, seizure, and coma. Early studies suggested that routine phosphate replacement is clinically beneficial for diabetic ketoacidosis.^{3,4} However, recent research failed to confirm this.^{1,5,6} We report a case of diabetic ketoacidosis who developed severe hypophosphatemia and respiratory failure and discuss the impact of hypophosphatemia.

CASE REPORT

A 39-year-old woman was admitted because of progressive shortness of breath.

The patient had been well until one month earlier, when general weakness gradually developed and wors-

ened, accompanied by weight loss of 6 to 7 kg, and polydipsia. Three weeks before admission, she began to complain of nausea. Two weeks before admission, she was examined by another physician and was told she had "hyperglycemia". On the morning of admission, she awoke with shortness of breath. During the day she was aware of a rapid heartbeat, lightheadedness, and sleepiness. Her mother observed that she became confused, and she was brought to this hospital and admitted. There was no history of travel abroad, contact with ill persons, drug abuse, seizures, focal neurologic deficits, fever, cough, diarrhea, or rash, and she reported that she did not smoke or drink alcohol.

The patient's parents were both still alive and in relatively good health. There was no family history of cancer, heart attack, stroke, rheumatologic, or endocrinologic disease.

She was 149 centimeters tall and weighs 49.1 kilograms. Her body mass index was 22.1, defined by weight in kg per meter square of height. On admission, her temperature was 35.3 °C, pulse rate was 115 beats per min-

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ute, and the respiratory rate 30 breaths per minute. Her blood pressure was 97/64 mm Hg. Oxygen saturation was 90 percent while the patient was breathing room air.

Physically, the patient appeared acutely ill with respiratory distress. The jugular venous pressure was normal. The lungs were clear, and the heart sounds were normal except for tachycardia. Abdominal examination was unremarkable. There was no peripheral edema, digital clubbing, or cyanosis. Neurologic examination was significant for symmetric weakness of all four limbs. The patient was alert and oriented but spoke in phrases of two to four words, rather than complete sentences.

Initial blood glucose was 402 mg/dL, arterial pH 6.906, PCO₂ 16.2 mmHg, PO₂ 170 mmHg, bicarbonate 3.2 mmol/L, and ketonemia (+++). The effective serum osmolality was 284.3 mOsm/kg. A chest radiograph revealed bilateral clear lung fields with normal mediastinal structures. An electrocardiography showed sinus tachycardia. The C-peptide level was less than 0.5 ng/mL and hemoglobin A_{1C} was 8.7%. Thyroid-stimulating hormone (TSH) was 0.149 μ IU/mL and free thyroxine (T4) was

13.2 pg/mL. A computed tomographic (CT) scan of the cranium revealed no significant abnormal density or mass effect. Echocardiographic study showed a normal left ventricular systolic wall motion. Other laboratory tests are listed in Table 1. The above findings were consistent with the diagnosis of diabetic ketoacidosis.

The patient was given fluids contain sodium and potassium intravenously, regular insulin 7 units as bolus followed by a continuous intravenous infusion of 5 units per hour and bicarbonate. Two hours after therapy, she became extremely short of breath, with use of accessory muscles. A second set of arterial blood gas analysis was obtained and revealed profound metabolic acidosis with a concomitant respiratory acidosis (pH 6.986, PCO₂ 21.9 mmHg, PO₂ 390 mmHg, bicarbonate 5.3 mmol/L, expected PCO₂ 15.9 mmHg, so there is a concomitant respiratory acidosis). On the basis of the blood gas results and the patient's respiratory status, a decision was made to intubate her and place her on mechanical ventilation. On the second day of admission, hyperglycemia and acidosis were corrected with total daily insulin dose of 74 units,

Table 1. Hematologic and blood biochemical values

Hematologic and blood chemical values					
Variable	Day 1	Day 2	Day 3	Day 5	Day 8
White cells (/mm ³)	14400		13100		124000
Hemoglobin (g/dL)	12.8		10.0		9.8
Platelets (/mm ³)	471 × 1000		244 × 1000		547 × 1000
Neutrophils	87.7		82		82.4
Lymphocytes	5.2		7		10.6
Monocytes	6.8		9		4.2
Phosphate (mg/dL)			0.3	2.0	4.4
Sodium (mEq/L)	131		134		147
Potassium (mEq/L)	1.3	3.0	2.2	3.7	3.0
Chloride (mEq/dL)	95				
Calcium (mg/dL)	9.4		8.0		7.9
Magnium (mg/dL)			2.6	2.9	
BUN (mg/dL)	20				28
Creatinine (mg/dL)	1.3				0.8
Albumin (g/dL)	4.3		2.4		
Bilirubin,T (mg/dL)			1.7		
Bilirubin,D (mg/dL)			0.0		
ALK-Pase (U/L)	170		155		
AST (U/L)	21		51		
ALT (U/L)	9		19		
LDH (U/L)			373		
CK (U/L)	154				106

but the patient became increasingly unwell, and the admission of oxygen was substantial. She was unable voluntarily to generate a vital capacity greater than 300 mL and required continuous assisted ventilation. General weakness persisted still, described as being unable to move her arms". Biochemical investigation revealed a severe hypophosphatemia of 0.3 mg/dL, and replacement therapy with potassium phosphate was initiated with 15 mmol in half saline administered intravenously as a continuous infusion over 12 hours in the first day and 120 mmol total in four days.

Three days after treated with potassium phosphate, the muscle weakness was much improved, and the forced vital capacity had increased to 500 mL. Weaning from the ventilator was started, and the patient was successfully extubated on the 13th hospital day. She recovered completely and was discharged after 4 weeks of hospitalization.

DISCUSSION

DKA is one of the most common medical emergencies in diabetic patients. The changes in serum phosphorus level in diabetic ketoacidosis have been described by previous investigators.^{4,5,7} Despite excessive urinary phosphorus excretion as a result of osmotic diuresis, an increased serum phosphorus level is common in diabetic ketoacidosis. The probable mechanism appears to be the shifting of phosphate from the intracellular to the extracellular compartment secondary to hyperglycemia and hyperosmolarity. After the initiation of insulin therapy, up to 90% of patients will have acute hypophosphatemia within 6 to 12 hours of beginning therapy.^{1,5} A combination of factors including fluid resuscitation, correction of acidosis, insulin therapy, and the use of bicarbonate make phosphate reenter the cells, thus lowering serum phosphate concentration. However, in some cases (as our patient), the presence of severe hypophosphatemia may develop even before treatment has been initiated. Some clues may help the clinician identify these patients. Usually, such patients are young, with new-onset type 1 diabetes. Vomiting has not been a prominent feature of their illness. Therefore, these patients can continue to drink large amounts of fluids,

which aggravates polyuria. All these factors extend the prodrome of diabetic ketoacidosis to weeks rather than the usual 2 or 3 days prior to seeking medical attention,⁸ and accordingly, there is proportionately greater opportunity to excrete more quantities of intracellular ion. Moreover, many of these cases have severe hypokalemia at the time when the diagnosis of diabetic ketoacidosis is made, despite the coexistence of metabolic acidosis.

Hypophosphatemia is considered to be moderate if the serum phosphate level is within 1.5 and 2.5 mg/dL, and severe if the serum phosphate level is less than 1.5 mg/dL.⁸ Symptoms of severe hypophosphatemia may mimic symptoms of associated underlying disease and therefore may not be recognized in a critically ill patient. Common manifestations include nausea, weakness, malaise, numbness, irritability, cardiomyopathy, confusion, convulsions, respiratory failure, rhabdomyolysis, and hemolytic anemia.⁸ Insulin resistance has also been reported in association with severe hypophosphatemia in diabetic ketoacidosis.⁹ Our patient suffered acute respiratory collapse and required mechanical ventilation, which may be the sequence of extra-pulmonary events in diabetic ketoacidosis and hypophosphatemia.¹⁰ The phosphate-depletion neuromuscular syndrome in man was first described in 1968. Furthermore, in patients who develop respiratory insufficiency, hypophosphatemia adversely affects diaphragmatic function.¹¹ The muscle weakness may arise from derangements seen in other systems. In the red cells, as the phosphate decreases, the concentrations of ATP and 2,3 diphosphoglycerate are all decreased, which may be implicated in muscle injury. The decreased level of 2,3 diphosphoglycerate causes a leftward shift of the oxygen dissociation curve and impairs oxygen release. Metabolic acidosis may occur in the presence of hypophosphatemia as a result of lower excretion of phosphate ions, therefore obliterating the capacity to excrete hydrogen ions. Usually, metabolic acidosis would be compensated by renal production of ammonia. However, in the hypophosphatemic patient, ammonia formation decreases as a subsequence of intracellular pH level rises. Hemolytic anemia results from rigidity of the red cell membrane. Hypophosphatemic cardiomyopathy and arrhythmias can contribute to respiratory insufficiency but are not much evidenced in this patient.

Theoretically, phosphate replacement therapy in diabetic ketoacidosis seems reasonable. However, prospective randomized studies failed to demonstrate any clinical benefits of routine phosphate replacement in diabetic ketoacidosis.^{1,5,6} In patients with cardiopulmonary compromise, anemia or severely depleted phosphate levels (< 1 mg/dL), phosphate replacement may still be indicated.¹² If the hypophosphatemia is mild and the patient is able to eat, oral therapy is preferred. It is a safer and more efficient mode of therapy. Parenteral replacement of phosphate should be reserved for patients with severe or symptomatic hypophosphatemia. However, it is imperative to recognize several important concepts before phosphate repletion. Phosphate is mainly an intracellular ion; less than 1% is present in the plasma. Therefore, serum phosphate levels do not reflect total body phosphate stores, and the response for any given dose is unpredictable. Especially if the patient has renal insufficiency, hyperphosphatemia could develop easily. Hypocalcemia, which is the consequence of hyperphosphatemia, can result in hypotension, metastatic calcification and impaired renal function.

Most phosphorus preparations contain a potassium salt base. One mL of the most commonly available phosphate solution (K₂PO₄) contains 4.4 meq of potassium and 3 mmol (93 mgs) of phosphate. Therefore, hyperkalemia may occur, especially in patients with a compromised renal function and oligouria. In the patients who present with hypophosphatemia and hyperkalemia, a phosphate solution contain sodium may be used. Serum phosphate, potassium and calcium levels need to be carefully monitored every 6 to 12 hours during phosphate re-

pletion.⁸

The phosphate preparations should be given in saline or dextrose solutions, not Lactated Ringers, which contains calcium and can result in calcium-phosphate precipitates.

Several protocols were developed for intravenous phosphate replacement (Table 2). The first prospective study to evaluate the efficacy and safety of parenteral phosphorus therapy in the severely hypophosphatemic patients administered 9 mmol phosphorus infused for 12 hours.¹³ More rapid replacement regimens were advocated in critically ill patients. In one study, intensive care patients with serum phosphate concentration between 1.27 and 2.48 mg/dL and patient with a concentration below 1.24 mg/dL were administered potassium phosphate 15 and 30 mmol respectively over 3 hours via a central line.¹⁴ Miller and colleagues suggested the maximal rate of phosphate infusion which was considered to be safe was 4.5 mmol/hr, or a total of 90 mmol per day.¹⁵ Once a serum phosphorus concentration of 2.0 to 2.5 mg/dL is achieved, switching to oral replacement therapy would be safer. Hypophosphatemic patients often are hypokalemic and hypomagnesemic, and these disorders should be corrected as well.

Severe hypophosphatemia is commonly seen in patients receiving treatment for diabetic ketoacidosis. Some patients even develop hypophosphatemia before treatment as described earlier. We should beware of those young, new-onset type 1 diabetic patients who develop symptoms of diabetes ketoacidosis many days before hospitalization. The phosphate depletion in these patients is usually severe and needs treatment.

Table 2. Protocols of phosphate replacement reported in the literatures

Authors	Case No.	Serum phosphate	Dose	Reference
Vannatta <i>et al.</i>	10	≤ 1 mg/dL	9 mmol of phosphorus infused continuously over 12 hours	13
Perreault <i>et al.</i>	17	1.27 ~ 2.48 mg/dL	15 mmol of phosphorus	14
	10	≤ 1.24 mg/dL	30 mmol of phosphorus Infused continuously via a central line over 3 hours	
Rosen <i>et al.</i>	11	≤ 2 mg/dL	15 mmol of phosphate over 2 hours or a total of 45 mmol per day	16
Miller <i>et al.</i>		≤ 1 mg/dL	4.5 mmol/hr or a total of 90 mmol per day	15

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