Disturbance of inorganic phosphate metabolism in diabetes mellitus: clinical manifestations of phosphorus-depletion syndrome during recovery from diabetic ketoacidosis

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Abstract: The acute effects of intracellular phosphate depletion and hypophosphatemia on organs and tissues in and during recovery from diabetic ketoacidosis (DKA) have been reviewed. When insufficient phosphate and/or oxygen are available for high energy phosphate synthesis, cell homeostasis cannot be maintained and cell integrity may be impaired. The clinical consequences are recognized as occasional cause of morbidity and mortality. Although phosphate repletion has not been routinely recommended in the treatment of DKA, physicians should be aware of these clinical conditions and phosphate repletion in such situations should be considered.

Keywords: high energy phosphates, hypoxia, fructose 1,6-diphosphate

Introduction

The phosphorus-depletion syndrome has been known to veterinary surgeons for many decades. In the 1960s, the phosphorus-depletion syndrome was first described in Man by Bloom and Flinchum, who also reported a case of muscle weakness and osteomalacia in a patient with excessive ingestion of nonabsorbable antacids containing magnesium–aluminum hydroxides, which limit gastrointestinal absorption of phosphorus. Lotz et al presented the effects of experimental phosphorus depletion in three normal volunteers and in three patients with parathyroid dysfunction during prolonged treatment with antacids. They observed a syndrome with hypophosphatemia, increased absorption of skeletal calcium and phosphorus, and clinical symptoms such as debilitation, anorexia, weakness, and bone pain. These reports were followed by more extensive research and reviews.

Recently, we have presented the evidence of the occurrence of a paradoxical imbalance in phosphate metabolism from the early onset of diabetes mellitus and have indicated that this imbalance may lead to a reduction of high energy phosphates and tissue hypoxia. These changes take place in cells and tissues in which the entry of glucose is not controlled by insulin and occur particularly in poorly regulated, though ambulatory diabetic patients in whom long-term vascular complications are more likely.6,7

In this article, we review the evidence suggesting the role of cellular phosphorus depletion and hypophosphatemia in the development of acute, occasionally life-threatening complications in hospitalized patients during treatment of diabetic ketoacidosis (DKA). The review is based on a search primarily using Medline (PubMed) and secondarily Embase, as well as information from reference lists.
Phosphorus plays an important role in several aspects of cellular metabolism, including ATP synthesis, which is the source of energy for many cellular reactions, and red cell glucose metabolism. Phosphorus is essential for the structure and function of many organelles and enzymes. Phosphorus deficiency can lead to impaired ATP synthesis, cell growth, and cell division.

Muscular manifestations

Muscular weakness is a common symptom of phosphorus deficiency. In addition to muscular weakness, patients with phosphorus deficiency may experience myalgia and rhabdomyolysis. Rhabdomyolysis can lead to kidney damage and can be life-threatening. Patients with phosphorus deficiency may also experience muscle stiffness and cramps.

Hematological manifestations

Anemia can be a complication of phosphorus deficiency. Patients with phosphorus deficiency may have reduced red blood cell counts, which can lead to symptoms of fatigue and shortness of breath. In addition to anemia, patients with phosphorus deficiency may experience increased bleeding tendencies.

Neurological manifestations

Neurological symptoms can occur in patients with phosphorus deficiency. Symptoms may include confusion, seizures, and altered mental status. In severe cases, patients may develop comas. Hyperphosphatemia or hypophosphatemia can affect brain function and lead to neurological symptoms.

Renal manifestations

Renal impairment can occur in patients with phosphorus deficiency. Patients may experience symptoms of renal insufficiency, including nausea, vomiting, and decreased urine output. In severe cases, patients may develop renal failure.

Dietary management

The management of phosphorus deficiency involves dietary intervention. Patients should be encouraged to consume foods rich in phosphorus, such as meats, dairy products, and nuts. In addition, patients should be encouraged to maintain adequate fluid intake to prevent dehydration.

Supplementation

In cases of severe phosphorus deficiency, supplementation with phosphorus may be necessary. The dose of supplementation will depend on the severity of the deficiency and the patient's overall health status.

Conclusion

Phosphorus deficiency is a common complication of many diseases. It is important for healthcare providers to recognize the signs and symptoms of phosphorus deficiency and to implement appropriate management strategies to prevent complications.
The arterioles in the cutaneous and splanchnic areas may be constricted, and blood flow will be shunted through biomicroscopically observable arteriolar–venular communications (thoroughfare channels; vascular pattern-change II) whereby blood flow bypasses the nutritive capillaries. The resulting ischemic hypoxia of glucose- and phosphate-starved muscle cells may lead to reduced ATP, resulting in membrane disruption and allowing myoglobin and creatine kinase isoenzyme MM to enter into the circulation.

**Myocardial manifestations**

Møller et al presented two patients with severe DKA, who showed elevations of the biomarkers troponin T and creatine kinase MB and initial electrocardiographic changes.
compatible with myocardial infarction. However, all successive investigations including coronary arteriography were normal. The concentration of plasma Pi was not reported. Hypophosphatemia is known to be associated with low levels of cellular ATP and impairment of human myocardial performance.\textsuperscript{34,35}

**Pulmonary manifestations**

Acute respiratory failure in DKA patients with severe hypophosphatemia has been reported, and normally good results have been reported with phosphate replacement.\textsuperscript{36,37}

**Renal manifestations**

Dehydration, volume depletion, renal hypoperfusion, and decreased intracellular tubular phosphate content often occur. Therefore, signs of renal tubular cell damage, as indicated by increased urinary excretion of enzymes from the brush border membrane such as increased urinary excretion of \(\beta_2\)-microglobulin, \(\gamma\)-glutamyltransferase, leucine aminopeptidase, and N-acetyl-\(\beta\)-D-glucosaminidase, are common. Cases of renal tubular acidosis have also been seen.\textsuperscript{38–40} These tubular cell disturbances may occur despite normal glomerular function.

**Gastrointestinal manifestations**

Nonspecific hyperamylasemia and abdominal pain are frequent findings during and after treatment of DKA with significantly negative correlation with plasma Pi.\textsuperscript{41–43} In a study of 12 patients with ketoacidosis, salivary, pancreatic isoamylases, and pancreas lipase were determined. Hyperamylasemia was present in six patients, of which, five showed simultaneous increases in all three specific pancreatic enzymes, and one had increased salivary isoamylases alone. In none of the patients, the clinical course or the time-concentration curves of pancreatic enzymes were consistent with acute pancreatitis.\textsuperscript{43}

**Discussion**

Despite the prevalence of hypophosphatemia, the aforementioned acute clinical consequences are not common. Some of the cited references are from the period prior to the advent of routine, low-dose insulin administration. However, as indicated, the early and severe hypophosphatemia associated with the recovery phase of DKA seems to be related to rapid uptake of glucose and Pi by the insulin-sensitive cells and tissues following the administration of insulin and correction of acidosis. In this situation, the insulin-insensitive cells may continue to be phosphate-starved and may suffer from affinity hypoxia with associated metabolic consequences. A flowchart indicating the most important factors leading to ATP deficiency in and during recovery from DKA is presented in Figure 2. Acidosis induces low red cell 2,3-DPG because of inhibition of phosphofructokinase and dehydration. Through redistribution of regional microcirculation and shunt flow, ischemic hypoxia may develop, which can be curtailed by rehydration.

As insulin begins to normalize glucose metabolism in the insulin-sensitive tissues, phosphorus enters into the cells and marked hypophosphatemia may develop. Hypophosphatemia slows the abolishment of affinity hypoxia (Figure 1). The two important elements, phosphorus and oxygen, for optimal ATP synthesis may thereby be limiting factors. Following the initial treatment of DKA, the cells of many organs and tissues may release enzymes, most likely because of this inhibition of energy metabolism. The resulting ATP depletion may lead to fluxes of Na\(^+\), K\(^+\), and Cl\(^-\) according to their gradients across the cellular membranes and with swelling of cells. Subsequently, Ca\(^{2+}\) may leak into the cells, activating phospholipases and the formation of eicosanoids, affecting the cytoskeleton, and initiating oxidant formation. The precise “point of no return” is unknown, but uncontrolled Ca\(^{2+}\) activity in the cell probably has an important role in initiating irreversible cell damage.\textsuperscript{44}

![Figure 2](https://www.dovepress.com/flowchart_ditzelelvang.png)

**Abbreviations:** ATP, adenosine triphosphate; ODC, oxyhemoglobin dissociation curve; 2,3-DPG, 2,3-diphosphoglycerate.
Diabetic patients with clinical symptoms of phosphate depletion and severe hypophosphatemia (<1.0 mg/dL); (tachyphylaxis, prolonged unconsciousness, rhabdomyolysis, respiratory failure, and ventricular tachycardia) and those with one or more defective oxygen transport mechanisms (severe anemia, chronic obstructive pulmonary disease, and congestive heart failure) should be repleted with phosphate. The symptoms and signs of phosphate depletion can vary, are nonspecific, and are usually seen in patients with multiple problems. This makes it difficult to identify phosphate depletion as the cause of the clinical manifestations. The response to phosphorus repletion with solutions of Pi is usually effective and safe.  

The organic phosphate, fructose 1,6-diphosphate (FDP), a key intermediate in glycolysis and the product of the major regulatory enzyme in the pathway (phosphofructokinase), has been suggested as an alternative. FDP acts as human bioenergy and can transport phosphorous into cells and, in a single report, FDP was shown to be more effective and safe than plasma Pi in restoring red cell 2,3-DPG in patients. Further studies on this subject are clearly needed before any conclusion can be reached.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**